VI-0521 (QNEXA®) ADVISORY COMMITTEE BRIEFING DOCUMENT

NDA 022580

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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EXECUTIVE SUMMARY

This document summarizes data in support of QNEXA® CR (controlled release) capsules, sponsored by VIVUS, Inc. of Mountain View, CA, for the treatment of obesity, including weight loss and maintenance of weight loss when used in conjunction with diet and exercise. If approved, QNEXA would be recommended for obese patients (body mass index [BMI] ≥30 kg/m^2) or overweight patients (BMI ≥27 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

Introduction

QNEXA, or VI-0521, is an investigational weight-loss therapy that is a novel combination of low-dose immediate-release phentermine (1/8 to 1/2 of marketed dose) and controlled-release topiramate (1/16 to 1/4 of marketed dose); both drugs are approved and marketed in the United States. The prescription use of these drugs spans more than 50 years for phentermine and more than 13 years for topiramate. Phentermine hydrochloride, at a labeled dose up to 37.5 mg/day (Adipex-P® package insert 2005; **Appendix 1**), is the most prescribed weight-loss drug with approximately 6.1 million prescriptions written in 2009 (Information Management System [IMS] data). The phentermine label, restricted to short-term management of obesity, limits its clinical application for the chronic treatment of obesity and weight-related co-morbidities. The primary mechanism of action of phentermine for weight loss is an anorectic effect occurring through the release of norepinephrine in the hypothalamus.

Topiramate is approved for treatment of seizure disorders at recommended doses up to 400 mg/day and for migraine headache prophylaxis at recommended doses up to 100 mg/day (Topamax® package insert 2009; **Appendix 1**). More than 9 million prescriptions were written in 2009 for topiramate (IMS data). Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety due to decreased gastrointestinal motility (Topiramate Summary Basis for Approval 1995), increased taste aversion (Supuran 2008), increased energy expenditure, and decreased caloric intake (Bray 2003; Richard 2000; Richard 2002; Picard 2000). Moreover, published clinical studies have shown that topiramate

monotherapy produces significant and dose-related weight loss in conjunction with clinically meaningful improvements in lipids, glycemic control, and blood pressure (Ben-Menachem 2003; Wilding 2004; Bray 2003). While the positive effects of topiramate on co-morbidities are primarily driven by weight loss, data from nonclinical and clinical studies provide evidence for additional positive effects of topiramate on glycemic parameters, blood pressure, and lipids (Stenlöf 2007; Astrup 2004) that are independent of weight reduction. Topiramate, however, is not approved for weight loss and is also associated with dose-limiting side effects, which prevent or limit its use as a single agent at the doses necessary to produce significant weight loss or cardiometabolic benefits.

The efficacy and tolerability of QNEXA is based on complementary, multi-targeted pharmacology that provides significantly greater weight loss, at lower doses, than has been previously demonstrated for the respective monotherapies at any dose level. The ability to use lower doses in combination that can achieve greater weight loss compared with the individual therapies is paramount to the positive risk/benefit relationship of QNEXA.

During the Advisory Committee meeting, VIVUS will focus on the efficacy and safety characteristics of QNEXA, the medical need and benefit-risk of the drug in obese patients and patients with obesity-related co-morbidities, the proposed Risk Evaluation and Mitigation Strategies (REMS) plan, and the proposed post-approval outcomes study with QNEXA. VIVUS plans to initiate pediatric studies in children to comply with the Pediatric Research Equity Act, post-New Drug Application (NDA) approval.

Medical Need

Results from the 2007-2008 National Health and Nutrition Examination Survey indicate that approximately 68% of adults in the United States are obese or overweight (Flegal 2010). Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, cancer, and type 2 diabetes (Must 1999; Poirier 2006). Epidemiological data indicate obesity and excess weight as factors associated with an increased risk of premature death (Adams 2006; Katzmarzyk 2003). Recent data suggest that if current increases in obesity rates

continue over the next decade, the health consequences of obesity will negate the gains in health benefits achieved through the reduction in smoking rates (Stewart 2009).

According to the National Institutes of Health (NIH) Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, "the initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline." The guidelines further state that, "The rationale for this initial goal is that even moderate weight loss, i.e., 10% of initial body weight, can significantly decrease the severity of obesity-associated risk factors" (National Institutes of Health 1998).

Unfortunately, currently approved pharmacotherapies are associated with <5% weight loss and are often poorly tolerated (Padwal 2007). At present, the only effective treatment for obesity is bariatric surgery; however, this approach has been reported to have significant complications in some individuals, such as nutritional deficiencies, infections and rarely, death. The inability of any approved medication to safely deliver sufficient and durable weight loss of ≥10% has spurred investigation into combination therapy to potentially fill the treatment gap between existing pharmacotherapies and bariatric surgery. Combination pharmacotherapy, in which drugs with distinct mechanisms are combined in a single formulation, have proved beneficial in related diseases, such as hypertension and type 2 diabetes. To avoid the health consequences predicted to result from the obesity epidemic in the United States, new approaches delivering more effective and better tolerated treatment are needed.

QNEXA Clinical Development Program

The QNEXA clinical development program for obesity consisted of three Phase 3 studies, four Phase 2 studies and ten Phase 1 studies, which altogether included more than 5000 subjects **(Appendix 3, Tables 43-45)**. Almost 3000 subjects were treated with QNEXA for 6 months or 1 year duration. Throughout the Phase 2 and Phase 3 program, subjects randomized in these studies were advised to initiate a lifestyle modification program using the Lifestyle, Exercise, Attitudes, Relationships and Nutrition (LEARN®) Program for Weight Management **(Appendix 7)**.

The study population evaluated in the QNEXA clinical development program included a range of adult subjects, from overweight (BMI >27 kg/m^2) to severely obese (BMI >60 kg/m^2), with a range of obesity-related co-morbidities, including type 2 diabetes, hypertension, and hypertriglyceridemia **(Section 3.3, Table 2)**. Subjects with depression or a history of depression (on and off antidepressant medication) were allowed to participate in the Phase 3 studies.

The initial selection of the respective doses of the two components in QNEXA tested in the proof-of-concept study (OB-201) was based on documented, published weight loss and tolerability results from studies of the individual agents (Bray 1998; Bray 1999; Bray 2003). Study OB-201 was a randomized, double-blind study in 200 obese adults that compared combination phentermine 15 mg and topiramate 100 mg (phentermine HCl administered in the morning and topiramate administered in the evening) with each component, at matching doses as monotherapy, and with placebo for 24 weeks. The phentermine/topiramate 15/100 mg dose and ratio of the combination therapy was found to be safe and well tolerated. Subjects treated with the phentermine/topiramate combination experienced a significantly greater and additive mean percent weight loss from baseline (10.7%) at Week 24 compared with subjects treated with phentermine 15 mg (4.6%), topiramate 100 mg (6.3%), or placebo (2.1%) based on an intent-to-treat–last observation carried forward (ITT-LOCF) analysis. The phentermine/topiramate combination resulted in a significantly higher proportion of subjects attaining ≥5% or 10% categorical weight loss at Week 24 (82%, 50%, respectively) compared with phentermine (38%, 14%) or topiramate (50%, 16%) monotherapy, or placebo (14%, 8%). The highest rate of retention and lowest rate of discontinuation due to adverse events (AEs) was observed for the phentermine/topiramate treatment arm.

In summary, the proof-of-concept study (OB-201) showed that the phentermine/topiramate 15/100 mg combination produced a magnitude of weight loss (~10%) that exceeded levels associated with current pharmacotherapies and met or surpassed Food and Drug Administration [FDA] criteria for approval of weight loss agents (Food and Drug Administration 2007; **Appendix 2**). Moreover, this combination achieved the recommended target weight loss goal of 10%, as established by the NIH guidelines. The efficacy and tolerability of

phentermine/topiramate 15/100 mg) observed in OB-201 established the target dose and component ratio to be tested in Phase 3 studies.

Based on study OB-201 findings a Phase 3 clinical trial program was designed to assess the safety and efficacy of a single-capsule, controlled-release formulation of phentermine/topiramate (QNEXA). The QNEXA single-capsule formulation contains immediate-release phentermine and controlled-release topiramate and is designed to mimic the time-sequenced daily dosing of the individual components studied in OB-201. The QNEXA formulation is designed so that peak exposure of each drug is separated by 7 to 8 hours such that phentermine exposure peaks near morning/early afternoon and topiramate exposure peaks near late afternoon/evening. The delivery of the topiramate component later in the day is expected to provide peak coverage for afternoon/evening hunger. Provision of QNEXA in a single daily dose is expected to improve overall compliance and ensure optimal morning and late afternoon delivery of active components.

The QNEXA Phase 3 clinical trial program investigated three dose levels—QNEXA Low dose (3.75/23 mg), Mid or recommended dose (7.5/46 mg), and Top dose (15/92 mg)—in severely obese subjects as well as in overweight and obese subjects with co-morbidities including type 2 diabetes, hypertension, and hypertriglyceridemia. The QNEXA Low- and Mid- dose levels were studied to characterize the QNEXA dose-response relationship and to identify a minimally efficacious dose. Availability of multiple dose levels allows dosing flexibility for different patient populations and individual treatment goals. The Phase 3 studies were discussed and agreed upon with the FDA through the end-of-Phase 2 meeting and the use of the Special Protocol Assessment process (studies OB-301 and OB-303).

Study OB-301 was similar in design to the proof-of-concept OB-201 study and was conducted to meet the requirements defined by the FDA for demonstration of QNEXA weight loss in excess of weight loss obtained with the individual components. Results of this study confirmed the efficacy and safety findings of the proof-of-concept study as well as the efficacy and safety of the QNEXA Mid and Top doses. Dose-related weight loss was observed in a population of 756 obese adults treated with QNEXA Mid or Top dose, phentermine alone, topiramate alone, or

placebo for 28 weeks. The maximal weight loss observed with the combination was greater, and was achieved at significantly lower doses, than the maximal weight loss observed with either agent alone or placebo.

The two pivotal Phase 3 studies (OB-302 and OB-303) were designed so that the number of subjects treated, the populations evaluated, the duration and design of the studies providing pivotal efficacy and safety data, and the endpoints evaluated, met guidelines agreed upon by the Sponsor and FDA's Division of Metabolism and Endocrinology Products. Study OB-302 was a 1-year, randomized, double-blind, placebo-controlled study that enrolled 1267 obese subjects with a lower BMI of 35 kg/m^2 and no upper limit. Both Class II (BMI >35 kg/m^2) and Class III (BMI >40 kg/m^2) obese adult subjects were included, with limited obesity-related co-morbidities. Comparisons for percent and categorical weight loss were made between QNEXA Low dose and Top dose with placebo after 56 weeks of treatment. Study OB-303 was a 1-year, randomized, double-blind study that enrolled 2487 overweight and obese adult subjects with two or more of the following weight-related co-morbid conditions: hypertension, elevated triglycerides, diabetes, fasting blood glucose >100 mg/dL, and/or waist circumference ≥102 cm for men or ≥88 cm for women. This study compared QNEXA Mid dose and Top dose with placebo after 56 weeks of therapy. The studies included ~20% of subjects with a history or presence of depression. Current use of antidepressant medications was allowed. Depression that was exacerbated or identified during the trial could be managed with new medications as needed while the subject remained in the study. (See **Section 4.2** for trial design and details of inclusion/exclusion criteria.)

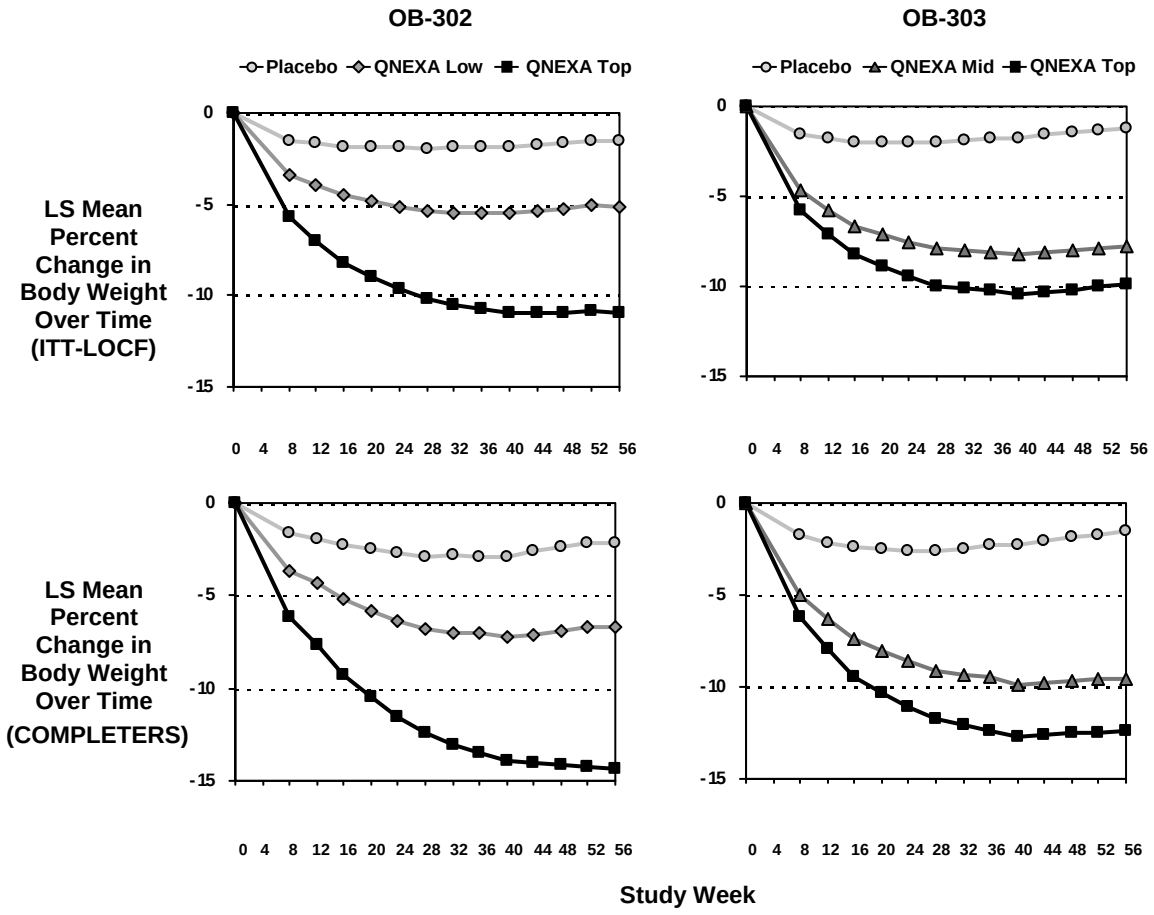
Efficacy in Phase 3 Pivotal Studies

Results across the pivotal Phase 3 studies were consistent with regard to weight loss, including time course of weight loss, as well as proportions of subjects achieving categorical weight-loss benchmarks, and were comparable to the results from the proof-of-concept study (OB-201). In subjects completing 1 year of treatment, an average weight loss of 13.4% (OB-302, 14.4%; OB-303, 13.2%) was achieved in subjects receiving QNEXA Top dose (15/92 mg) compared with subjects receiving placebo (OB-302, 2.1%; OB-303, 2.4%). Weight loss was also achieved

in subjects receiving QNEXA Mid dose (7.5/46 mg; OB-301, 10.7%; OB-303, 10.5%) and Low dose (3.75/23 mg; OB-302, 7.0%).

Treatment with QNEXA, at all three dose levels, resulted in statistically significant percent and categorical weight loss (from baseline to end of study) compared with placebo treatment (**Figure 1)**.

Figure 1. Percent Weight Loss From Baseline Over Time (ITT-LOCF and Completers Sets)



p<0.0001 vs placebo at all time points for all doses.
ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Significant weight loss with QNEXA was observed at 4 weeks and continued progressively over the course of the 1-year trials. Moreover, the observed mean and categorical weight loss at 1 year

substantially exceeded the FDA and NIH guidance for weight management products. Overall, 45% to 70% of all QNEXA-treated subjects achieved the 5% weight-loss threshold. The Phase 3 studies demonstrated a dose relationship with QNEXA therapy and support three dosing levels that provide a flexible dose regimen for QNEXA. Subgroup analysis based on subject baseline demographic characteristics indicated that weight loss achieved with QNEXA therapy was unaffected by race, sex, age or baseline BMI. Weight loss with QNEXA was primarily attributed to a reduction in fat mass and not lean body mass and reductions in subject mean waist circumference were consistently greater in subjects treated with QNEXA, relative to placebo, across trials.

Effects of Weight Loss on Weight-related Co-morbidities

Disease subgroup analyses based on presence of hypertension, hypertriglyceridemia, or diabetes co-morbidities in subjects at baseline indicated similar weight loss between disease and non-disease subjects treated with QNEXA.

The effect of QNEXA treatment on important weight-related co-morbidities was assessed throughout the clinical program in the whole study population regardless of baseline status (patients with and without co-morbidities), and then specifically, in pre-existing disease populations, such as subjects with hypertension, hypertriglyceridemia, and type 2 diabetes. Significant and dose-related improvements in cardiovascular, metabolic, glycemic and inflammatory endpoints, were obtained with QNEXA therapy and maintained throughout the 56 weeks of treatment, as indicated by assessment of the broad ITT population. At 6 months and 1 year, QNEXA therapy resulted in consistently observed, statistically significant decreases from baseline in systolic and diastolic blood pressure. In study OB-303, QNEXA Mid dose and Top dose reduced systolic blood pressure by 4.7 and 5.6 mm Hg, respectively, compared with a 2.4 mm Hg reduction obtained with placebo. Triglycerides, high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) were each significantly reduced from baseline compared with placebo across the Phase 3 trials with QNEXA therapy. Hemoglobin A_{1c} (HbA_{1c}), and fasting glucose were also consistently and significantly reduced from baseline, compared with placebo across Phase 3 trials. In study OB-303 in which the majority of subjects were not

diabetic at baseline, QNEXA Top dose resulted in a least squares (LS) mean HbA_{1c} reduction of 0.1% from baseline at Week 56 compared with an increase of 0.1% obtained with placebo. Fasting serum glucose levels were also reduced from baseline in subjects treated with QNEXA Mid dose and Top dose by 9.7 and 11.9 mg/dL, respectively, compared with a reduction 5.6 mg/dL with placebo.

QNEXA Mid-dose and Top-dose therapy also resulted in significantly reduced liver enzyme levels (alanine transaminase [ALT] and aspartate transaminase [AST]) from baseline compared with placebo. In study OB-303, ALT levels decreased from baseline with QNEXA Mid-dose and Top-dose therapy by 4.0 and 3.3 mU/mL, respectively, compared with a reduction of 0.8 mU/mL with placebo.

Levels of high-sensitivity (hs)-CRP were significantly reduced from baseline in the QNEXA Mid- and Top-dose groups. From a mean baseline value of 7.28 mg/L (all groups), subjects on QNEXA Mid and Top dose achieved a 39% reduction in hs-CRP by Week 56. In those subjects with a baseline hs-CRP>3 mg/L (group mean 10.15 mg/L) the QNEXA Mid- and Top-dose groups achieved hs-CRP reductions of 4.6 and 4.4 mg/L, respectively.

Analysis of prespecified subgroups of subjects with hypertension, hypertriglyceridemia or diabetes at baseline in study OB-303 indicated that significant and greater absolute improvements from baseline in cardiovascular, glycemic, metabolic and inflammatory endpoints could be attained in obese QNEXA-treated subjects with disease versus without disease. QNEXA-treated hypertensive subjects in study OB-303 demonstrated significant and clinically meaningful improvements in systolic (9.1 mm Hg) and diastolic (5.8 mm Hg) blood pressure compared with placebo-treated hypertensive subjects. Subjects with hypertriglyceridemia and treated with QNEXA in study OB-303 demonstrated significant and clinically meaningful improvements from baseline in levels of triglycerides (reduced 25.6%), HDL-C (increased 10.7%), and total cholesterol (reduced 7.8%).

QNEXA-treated diabetic subjects in OB-202/DM-230 (advanced diabetes) and OB-303 demonstrated significant and clinically meaningful reductions in HbA_{1c} (1.6% in OB-202/DM-

230 and 0.4% in OB-303) and other glycemic endpoints, including fasting glucose and post-prandial glucose (measured in OB-202/DM-230 only).

In analyses of all subjects treated in study OB-303 (ITT-LOCF), both QNEXA Mid- and Top-dose treatment resulted in statistically significant and clinically meaningful reductions in fasting insulin and insulin resistance, important markers in the development of type 2 diabetes. Moreover, among subjects without a diagnosis of type 2 diabetes at study entry, progression to type 2 diabetes, based on fasting glucose levels of ≥126 mg/dL or glucose levels of ≥200 mg/dL during oral glucose tolerance test evaluations, occurred in 9.9% of placebo-treated subjects compared with 6.6% of QNEXA-treated subjects (relative risk 0.66; 95% confidence interval 0.53-0.83). Thus, QNEXA treatment resulted in a 41% decrease in the annualized incidence of type 2 diabetes in these study subjects.

Examination of liver function test values after 1 year in subjects with elevated ALT values at baseline (upper quartile) indicated that subjects treated with QNEXA Mid and Top dose demonstrated significantly greater improvements in ALT values from baseline compared with subjects treated with placebo (16.7 and 16.3 mU/mL reduction for QNEXA Mid dose and Top dose compared with 9.2 mU/mL reduction with placebo).

Assessment of the change from baseline at study endpoint in medications taken by subjects for treatment of hypertension and diabetes revealed that improvements in disease endpoints following QNEXA treatment were also associated with significant concomitant reduction in antihypertensive and antidiabetic medications, compared with placebo. In study OB-303, among subjects with hypertension, QNEXA Mid dose and Top dose resulted in net decreases from baseline at Week 56 of 6.6% and 10.5%, respectively, in the use of antihypertensive medications compared with a 3.4% net increase in the use of antihypertensive medications among hypertensive subjects treated with placebo. At Week 56, diabetic subjects in study OB-303 treated with QNEXA Mid dose or Top dose increased use of diabetes medications from baseline by 1.5% and 0.6%, respectively, compared with the more pronounced increase in use of diabetes medications of 12.1% by subjects treated with placebo.

Assessments of Quality of Life using the Impact of Weight on Quality of Life (IWQOL) and Short Form (SF)-36 questionnaires during the QNEXA clinical development program indicated significant and greater improvement from baseline in health, daily function, and quality-of-life scores in subjects treated with QNEXA compared with subjects receiving placebo.

Safety

The overall safety of QNEXA was based on the integrated safety data obtained from the three pivotal Phase 3 studies (OB-301, OB-302, and OB-303) and the two supportive Phase 2 studies (OB-202 and DM-230). Integrated analysis cohorts, a 6-month cohort and a 1-year cohort, were created to facilitate separate assessments of the safety and tolerability profile of QNEXA in the context of relatively short-term use and chronic, or relatively long-term, use. The integrated analyses demonstrated that QNEXA Low dose, Mid dose, and Top dose were safe and generally well tolerated by subjects. Overall study retention was significantly higher in all 1-year studies for QNEXA treatment arms compared with placebo.

The safety and tolerability profile of QNEXA was also evaluated in the context of the known adverse effects indicated in the approved component labels of the individual agents used as monotherapy for various indications. The frequency and severity of treatment-emergent adverse events (TEAEs) observed within the QNEXA clinical program were consistent with approved product labels for phentermine and topiramate. No unexpected toxicity related to the respective components was observed.

The primary analysis of safety was performed on the 1-year cohort to maximize duration of exposure to QNEXA. The overall incidence of TEAEs was higher in the active treatment groups than in the placebo group (placebo, 76.0%; QNEXA Low dose, 80.0%; Mid dose, 85.1%; Top dose, 87.2%). Most of the TEAEs were mild or moderate in severity. The incidence of severe TEAEs was greater for QNEXA-treated subjects (placebo, 8.6%; Low dose, 10.4%; Mid dose, 11.0%; Top dose, 12.5%). However, the incidence of treatment-emergent serious adverse events (SAEs) for the 1-year cohort was low and similar for the treatment groups (placebo, 3.3%; Low dose, 2.5%; Mid dose, 2.8%; Top dose, 3.6%). One death occurred during the studies, a placebo-treated subject who suffered cardio-respiratory arrest in study OB-303. No differences between

QNEXA and placebo treatment in the incidence of SAEs in particular system organ classes were noted. The incidence of cardiac SAEs was not increased in QNEXA-treated subjects relative to placebo-treated subjects.

The most frequently reported TEAEs with QNEXA treatment were paresthesia (17.0%), dry mouth (16.6%), constipation (15.1%), upper respiratory tract infection (13.5%), nasopharyngitis (10.0%), and headache (9.8%). The incidence of paresthesia, dry mouth, constipation, dysgeusia, insomnia, irritability, and alopecia was higher in the active treatment groups than in the placebo group and increased in a dose-related manner. Overall study retention was consistently higher for all QNEXA arms compared with placebo; however, the percentages of subjects who discontinued study drug due to an AE were higher in the active treatment groups than in the placebo group (placebo, 8.5%; Low dose, 11.7%; Mid dose, 11.6%; Top dose, 17.5%).
The topiramate and phentermine approved labels contain several categories of AEs that are observed in greater frequency or severity and which may also represent important markers of risk for each respective compound. To ensure that these and other AEs of interest (targeted medical events) were clustered and assessed in a conservative and comprehensive manner, selected events were identified at the preferred term level and also categorized by class and subclass. The classes of targeted medical events included psychiatric disorders, cognitive disorders, psychomotor disorders, drug abuse/withdrawal, menstrual disorders, ophthalmic disorders, and cardiac disorders. Subclasses of the psychiatric disorders class included sleep disorders, depression, anxiety, and suicide/self-injury. Subclasses of the cognitive disorders class included attention, language, memory impairment, and other cognitive disorders. Subclasses of the cardiac disorders class included cardiac arrhythmia and ischemic heart disease.

From the summary of targeted medical events, the incidence of TEAEs clustered and categorized as sleep disorders was higher in the QNEXA Top-dose group (10.8%) than in the placebo group (5.7%). Most of the sleep disorder TEAEs were related to insomnia and were mild in severity (placebo, 3.7%; QNEXA Top dose, 6.2%). The incidence of TEAEs in the depression (standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ]) subclass, which included affect lability, apathy, crying, depressed mood, depression, dysthymic disorder, mood altered, and tearfulness, was overall higher in the Top-dose group (7.7%) than in the

placebo group (3.4%); the incidence of TEAEs in the depression subclass was similar for the Mid-dose group (3.8%) and placebo group (3.4%). The incidence of TEAEs in the anxiety subclass was higher in the QNEXA groups than in the placebo group (placebo, 2.6%; Low dose, 4.6%; Mid dose, 4.8%; Top dose, 7.9%).

None of the anxiety or depression TEAEs in the 1-year cohort was considered to be SAEs. The incidence of moderate or severe depression and depressed mood were similar between treatment groups. Importantly, there was no difference in the use of new psychiatric or antidepressant medications during the study between active treatment groups and placebo.

The incidence of TEAEs categorized as cognitive disorders, including the incidences of attention TEAEs and memory impairment TEAEs, was higher in the QNEXA Top-dose group (3.5% and 2.5%, respectively) and Mid-dose group (2.0% and 1.8%, respectively) than in the placebo group (0.6% for each disorder). The incidence of language TEAEs and other cognitive disorders was low overall but higher in the Top-dose group (1.2% and 1.8%, respectively) than in the placebo group (0.1% and 0.3%, respectively). The TEAEs categorized as cognitive disorders were primarily mild in severity. There were no serious adverse events reported for cognitive disorders class.

The incidence of TEAEs categorized as ophthalmic disorders and menstrual disorders was low and similar for the treatment groups. The incidence of TEAEs categorized as psychomotor disorders was low overall but higher in the QNEXA Top-dose group (0.8%) than in the placebo group (0.1%). No subject in the 1-year cohort had a drug abuse/withdrawal TEAE.

The incidence of TEAEs in the cardiac arrhythmia subclass was higher in the QNEXA Top-dose group (4.7%) and Mid-dose group (4.2%) than in the placebo group (1.8%). Palpitations, increased heart rate, and tachycardia represented 36 of the 41 cardiac arrhythmia TEAEs in the 1-year cohort. Palpitations and increased heart rate are expected and dose-related side effects of phentermine and phentermine-containing products. The cardiac arrhythmia TEAEs were primarily mild or moderate in severity and were serious for 4 (0.3%) subjects in the placebo group, 2 (0.4%) subjects in the Mid-dose group, and 2 (0.1%) subjects in the Top-dose group.

Serious cardiac adverse events were examined in all subjects included in the Integrated Safety Analysis of the NDA. Overall, there were eight cardiac SAEs in the QNEXA groups (N=2559) and nine in the placebo group (N=1719). The relative risk was 0.60 (95% CI: 0.23-1.54), QNEXA vs. placebo. The incidence of TEAEs in the ischemic heart disease subclass was low (0.4% overall) and similar for the treatment groups.

Various analyses and studies have been conducted to assess QNEXA cardiovascular safety. Results from the Thorough QT study (study OB-118) demonstrated that QNEXA treatment does not cause QT prolongation; and the echocardiographic data from study OB-201 showed that QNEXA treatment did not result in changes in heart valve morphology. In the 1-year cohort, small mean increases in heart rate were observed in the QNEXA treatment groups (0.6-1.6 bpm at the Top dose) compared with placebo treatment groups. QNEXA therapy was associated with consistent reductions in systolic and diastolic blood pressure compared with placebo across all studies, most notably in patients with hypertension at baseline. The rate-pressure product (RPP) was also reduced during treatment; there were no differences in RPP between the placebo and QNEXA treatment groups. The percentages of subjects with new/abnormal findings on auscultation of the heart, such as abnormal heart sounds and murmurs, were low and similar in QNEXA treatment and placebo groups. From the individual studies, no important differences among the treatment groups in changes in electrocardiogram (ECG) parameters or physical examination findings at the final study visit were observed.

As a result of concerns over the potential effects of centrally acting weight-loss agents (and certain antidepressants and anticonvulsants) on suicidality, the FDA requires labeling for all anticonvulsants, including topiramate, regarding a potential increased risk of suicidal behavior and suicidal ideation with these agents. Although the doses of topiramate studied are well below those approved for the treatment of seizures (400 mg) there remains a need for formal, prospective assessments of depression and suicidality at baseline and all study visits.

The Patient Health Questionnaire (PHQ-9) instrument was used at baseline and at each visit to assess mood and depression. A decrease in score can be associated with a reduction in the presence and severity of symptoms of depression. In all studies, all treatment groups had mean

decreases in the PHQ-9 total score. No differences were noted among treatment groups in mean changes in the PHQ-9 score. The summary of worsening shifts in PHQ-9 depression severity for the integrated 1-year cohort by treatment group likewise did not reveal any treatment-related patterns. Therefore, with regard to PHQ-9-assessed depression, the effects of treatment with QNEXA were not distinguishable on a population basis from effects of placebo.

The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to prospectively assess suicidal behavior and ideation in the Phase 3 trials at every subject visit. During the studies there were no occurrences of suicidal behavior or attempts and no occurrences of serious suicidal ideation. In addition, there were no significant differences across treatment groups in emergence or worsening of suicidal ideation. In an analysis of the intensity of suicidal ideation throughout the trials, overall frequency of suicidal ideation was low; the highest levels were seen at baseline.

Overall, there were no differences between QNEXA treatment and placebo groups in incidence of serious laboratory-related AEs or study drug discontinuations due to laboratory-related AEs. Some differences among the treatment groups in changes in safety laboratory parameters of potassium (K+) and bicarbonate were noted.

In the 1-year cohort, the percentage of subjects with serum bicarbonate values <17 mEq/L persistence was higher in the QNEXA (Low dose, 1.3%; Mid dose, 0.2%; Top dose, 0.7%) treatment groups than in the placebo group (0.1%). Given that the risk for metabolic acidosis increases with reductions in serum bicarbonate and can be compounded by co-medications, the risk for metabolic acidosis with QNEXA in the presence of metformin was investigated. No increased risk for metabolic acidosis was found when QNEXA was co-administered with metformin.

No subject in the placebo or QNEXA Low-dose groups and few subjects in the QNEXA Mid-(0.2%) and Top-(0.1%) dose groups had serum potassium <3.0 mmol/L persistence concurrent with a decrease of >0.5 mmol/L from baseline. Two subjects had elevations in liver transaminases in the presence of elevated bilirubin that occurred concurrently with SAEs of cholelithiasis, which resolved on treatment. These effects were dose related and consistent with topiramate's inhibitory effects on carbonic anhydrase enzymes.

Both topiramate and phentermine are currently labeled as Pregnancy Category C. QNEXA has not demonstrated selective developmental toxicity, including teratogenicity, at ~6-fold and ~13-fold above the recommended human dose (RHD = QNEXA Mid dose), in rats and rabbits, respectively. The QNEXA clinical program contained 34 pregnancies that occurred in the QNEXA and placebo treatment arms. None of the pregnancies that occurred during QNEXA therapy was associated with adverse outcomes. All births have been characterized as healthy and normal. The proposed label and REMS plan will contain detailed information regarding the use of QNEXA in women of child-bearing potential. Because weight loss during pregnancy is not desirable, QNEXA (or any other weight loss medication) is not recommended for use in patients who are pregnant or plan to become pregnant. Adequate contraception should be used in women of child-bearing potential for the prevention of unintended pregnancy, as weight-loss may improve fertility. VIVUS also plans to participate in a pregnancy registry in obese subjects of child-bearing potential.

A REMS program has been developed by VIVUS to inform healthcare providers (HCPs) and patients of the potential risks associated with QNEXA and to mitigate these risks. This program includes education about the appropriate and safe use of QNEXA and the importance of appropriate patient selection. In addition, risks for the following conditions are discussed: psychological or cognitive AEs, certain types of glaucoma, metabolic acidosis, and pregnancy and contraception issues. The REMS program has been designed to communicate information to HCPs and patients by means of a Medication Guide, Communication Plan, and a Timetable for Assessments. It also includes a plan to assess both prescriber and patient understanding of the REMS messages. VIVUS will routinely monitor the HCP Training Program database. (See **Section 10** and **Appendix 9** for details of the REMS program).

Post-Approval Outcomes Trial

As part of a program for post-marketing surveillance and pharmacovigilance VIVUS has planned an outcomes trial to assess long-term safety and efficacy of QNEXA on cardiovascular as well as weight-related morbidity and mortality outcomes. This post-approval outcomes trial will be a randomized, placebo-controlled, multi-center trial including 8000 to 10,000 at-risk obese

subjects with co-morbidities and/or history of cardiovascular disease. The planned average duration of treatment will be approximately five years. The proposed primary endpoint will be composite major adverse cardiac events (MACE) (myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina or exacerbation of congestive heart failure) and weight-related cancer and mortality. Additional secondary endpoints will include rates of individual MACE events, weight loss and maintenance of weight loss, cardiovascular and metabolic risk factors, and quality-of-life and pharmacoeconomic endpoints.

Conclusions

Current pharmacotherapies used in conjunction with diet and exercise can achieve weight loss of approximately 5%, while surgical interventions, which can achieve >15% weight loss, are invasive and not without postsurgical complications. There is currently no effective, noninvasive, treatment that is capable of achieving a meaningful degree of weight loss of ≥10%, which has been established by experts to be the goal of weight loss that commensurate with a significant decrease in the severity of obesity-associated risk factors. There is, therefore, a treatment gap for noninvasive therapies that achieve weight loss in the range of 10% to 15%.

QNEXA is comprised of low doses of two approved agents (phentermine and topiramate) that produce weight loss through unique and complementary mechanisms. The weight loss response with the combination is greater, and is achieved at significantly lower doses, than the maximal response attained with either agent alone.

QNEXA is highly effective for weight loss across a broad population of obese subjects, with a similarly broad range of obesity-related co-morbidities. Both by measures of central tendency and response rates for various degrees of weight loss from baseline, QNEXA was found to be markedly effective in a high proportion of subjects in promoting durable weight reduction and in ameliorating the course of obesity-related co-morbidities. The proportion of QNEXA-treated subjects attaining ≥10% total body weight loss was comparable across increasing BMI categories at baseline up to a BMI >50 kg/m^2. The benefits of weight reduction with QNEXA treatment on cardiovascular, metabolic, and glycemic parameters were greatest for subjects with the most marked disease characteristics at baseline.

QNEXA treatment was safe and generally well tolerated by overweight and obese subjects with and without weight-related co-morbidities. The most commonly observed adverse events, notably paresthesia, dry mouth, dysgeusia, and insomnia, are well known and characterized side effects of one or the other component agent and do not represent novel side effects engendered through the combined pharmacology of the two drugs. There was a small increase in the incidence of depression for the Top dose that was driven predominately by mild to moderate events. These events occurred early and resolved without sequelae. Importantly, PHQ-9 and C-SSRS results did not identify a significant increase in QNEXA-treated subjects for development of depression or occurrence of suicidal behavior or ideation.

For obese individuals, the adverse impact of obesity on health and quality-of-life outcomes is well documented. Based on the results of the IWQOL and SF-36 questionnaires conducted in support of the QNEXA NDA, durable weight loss and substantial improvements in weight-related co-morbidities appear to be associated with significant improvement in health-related and quality-of-life outcomes for QNEXA-treated subjects.

QNEXA represents a significant advancement in the medical treatment of obesity and management of weight-related co-morbidities, such as hypertension, type 2 diabetes, and dyslipidemia. If left unchecked, the adverse impact of obesity on health outcomes is expected to be unprecedented. The ability of QNEXA to produce durable weight loss can be expected to contribute significantly toward ameliorating some of the consequences of obesity and weight-related co-morbidities. On the basis of the efficacy and safety data from clinical studies, QNEXA demonstrates a favorable benefit-risk profile when used as an adjunctive measure in the management of obesity.

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5-HT	Serotonin
ACS	acute coronary syndromes
AE	adverse event
AHI	apnea/hypoxia index
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time zero to infinity
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BrAC	breath alcohol concentration (level)
CAD	coronary artery disease
CI	confidence interval
CK	creatine kinase
CKMB	creatine kinase myocardial band
CL_{cr}	creatinine clearance
cm	Centimeter
C_{max}	peak plasma concentration
COM	combination of phentermine and topiramate
CR	controlled release
CRP	C-reactive protein
hs-CRP	high-sensitivity–C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CVA	cerebrovascular accident
CYP	cytochrome P450 (enzyme)
DBP	diastolic blood pressure
D/C	discontinued
ECG	electrocardiogram
EEG	electroencephalogram
ET	early termination
F	Fahrenheit

FDA	Food and Drug Administration
fen-phen	fenfluramine and phentermine
GABA	γ-aminobutyric acid
GI	Gastrointestinal
HbA_{1c}	hemoglobin A_{1c}
HCl	hydrochloride
HCP	healthcare provider
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment of insulin resistance
IC_{50}	half maximal inhibitory concentration
IMS	Information Management System
INR	international normalized ratio
ITT	intent-to-treat (population)
IU/L	international units per liter
IWQOL	Impact of Weight on Quality of Life Questionnaire
IV	Intravenous
KAB	Knowledge, Attitude, Behavior (surveys)
K/μL	thousands per microliter
kg	kilogram
kg/m^2	kilogram per meter squared (unit of measure for body mass index)
K_i	inhibition constant
LDL-C	low-density lipoprotein cholesterol
LEARN®	Lifestyle, Exercise, Attitudes, Relationships and Nutrition
LFT	liver function test
LOCF	last observation carried forward (analysis)
LS	least squares
MACE	major adverse cardiac event
MAO	monoamine oxidase
μg	Microgram
μIU/mL	micro-international units per milliliter
mEq/L	milliequivalent per liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/day	milligrams per day
mg/dL	millgrams per deciliter
mg/L	milligrams per liter
mL	Milliliter

mL/min	milliliter/minute
MI	myocardial infarction
mm Hg	millimeter mercury
mmol	millimoles per liter
MRI	magnetic resonance imaging
msec	millisecond
NA	not available
NDA	New Drug Application
NE	norepinephrine
ng/mL	nanograms per milliliter
NIH	National Institutes of Health
NOS	not otherwise specified
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
PD	Pharmacodynamic
PHQ-9	Patient Health Questionnaire
phen	commercially available phentermine
PHEN	phentermine hydrochloride in VIVUS's proprietary capsule formulation
PK	pharmacokinetic
popPK	population PK
PR	The period in the tracing of the electrocardiogram between the start of the P wave and end of the R wave
QD	once daily
QNEXA Top	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (15 mg) and topiramate (92 mg), the "Top" dose
QNEXA 11.25/69	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (11.25 mg) and topiramate (69 mg), the "three-quarter" dose
QNEXA Mid	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (7.5 mg) and topiramate (46 mg), the "half," "Mid," or recommended dose
QNEXA Low	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (3.75 mg) and topiramate (23 mg), the "Low" dose
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBANS	Repeatable Battery for Assessment of Neuropsychological Status

REMS	Risk Evaluation and Mitigation Strategies
RHD	recommended human dose
RPP	rate-pressure product
RR	period in the tracing of the electrocardiogram between the two R waves
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-36	Short Form-36
SMQ	standardized Medical Dictionary for Regulatory Activities (MedDRA) query
SNRI	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
ST	segment in the tracing of the electrocardiogram between the start of the S wave and the end of the T wave
TC	total cholesterol
TEAEs	treatment-emergent adverse events
TG	triglycerides
TIA	transient ischemic attack
T_{max}	time to peak plasma concentration
TME	targeted medical event
Tmt	Treatment
tpm	commercially available topiramate
TPM	topiramate in VIVUS's proprietary capsule formulation
U/L	units per liter
ULN	upper limit of normal
vs	versus

1 INTRODUCTION

1.1 Medical Landscape

Obesity is widespread in the United States today. National Health and Nutrition Examination Survey data from 2007-2008 indicate that approximately 68% of US adults are obese or overweight, and one-third of the adult population has a body mass index (BMI) ≥30 kg/m^2 (Flegal 2010). Analysis of these data further indicates that people with a BMI between 30 and 40 kg/m^2 lose between 1 and 7 years of life expectancy, and those with a BMI >45 kg/m^2 lose up to 13 years (Fontaine 2003).

Obesity is a psychologically and economically debilitating disorder for which both complex metabolic and behavioral components have been identified. During most of human evolution, humans confronted food scarcity and engaged in high levels of physical activity (Bellisari 2008). Humans evolved the ability to store body fat when opportunities to consume excess energy arose, and developed elaborate and complex genetic and physiological systems to protect against starvation and to defend stored body fat (Bellisari 2008). That obesity has a biologic basis is well accepted, as single genes contributing to obesity have been discovered and inheritance of the condition has been demonstrated in some patients (Bellisari 2008). This complex biology of obesity may explain observations that responses to obesity therapies vary across populations of obese patients, and that most obese individuals do not achieve sustained weight reduction without supplemental pharmacological or surgical intervention.

Obesity is associated with an increased risk of premature death, primarily caused by a variety of co-morbidities, including dyslipidemia, cardiovascular disease, hypertension, cancer, and type 2 diabetes (Flegal 2007; Must 1999; Poirier 2006). Obese individuals have medical costs approximately 30% greater than their normal-weight peers; in the United States the aggregate of these costs is estimated at $23 billion per year (Withrow 2010). Even a modest weight loss of 5% to 10% can result in a marked improvement in obesity-related metabolic and cardiovascular risk factors (Goldstein 1992; Pasanisi 2001; Douketis 2005). Diet, exercise, and behavior modification without pharmacologic enhancement are standard treatments for obesity that have

demonstrated limited efficacy. To avoid the health consequences predicted to result from the obesity epidemic in the United States, more effective and better tolerated therapies for obesity are required.

There are three oral medications currently available for treatment of obesity:

- *Sibutramine* achieves a mean weight loss of 3% to 4% during the first 6 to 12 months of therapy. However, 50% or more of the weight is regained after 2 years of continuous therapy. It is associated with severe cardiovascular adverse events (AEs) and carries a strong warning label in United States.

- *Orlistat*, available either in prescription or in over-the-counter formulations, achieves a mean placebo-adjusted weight loss of 3% to 4% at 1 year. Extension of therapy to 2 years results in the regain of one-third of the lost weight. Orlistat is associated with substantial gastrointestinal side effects that are recognized to limit its use and compliance.

- *Phentermine* monotherapy (up to 37.5 mg) achieves a mean weight loss of 4% to 5%. It is approved only for short-term (3 months) use. Phentermine is the most widely prescribed weight loss agent with 6.1 million total prescriptions written (branded and generic) in 2009, up 14% over 2008 (Information Management System [IMS] data).

Current medications approved by the Food and Drug Administration (FDA) for treatment of obesity are generally associated with only low to moderate weight loss, are often poorly tolerated, are transiently efficacious, and exhibit variability of response among patients. To date, no oral agent has demonstrated compelling evidence of beneficial long-term outcomes. A possible explanation for the failure of oral agents to provide such long-term benefits is that a higher threshold of weight loss is required in order to effect lasting co-morbidity improvement. Significantly greater and more lasting weight loss of 16% to >30% has been achieved with various bariatric surgery procedures, with concomitant reductions in related co-morbidities and mortality, but patients undergoing these operations must be prepared to handle the risks and stresses associated with this type of invasive surgical intervention (Colquitt 2009).

To reduce the health consequences predicted to result from the obesity epidemic in the United States, new noninvasive therapies are required that safely fill the existing treatment gap between

current pharmacotherapies providing <5% weight loss and bariatric surgery. The high recidivism of obesity with oral therapies, behavioral modification, or surgical approaches suggests that an oral therapy that can affect multiple mechanisms is needed to improve efficacy, increase the probability that patients will respond to therapy, and provide a durable response.

1.2 Rationale for QNEXA Therapy

QNEXA is an investigational, orally administered, once-daily weight loss therapy that contains a proprietary low-dose combination of immediate-release phentermine hydrochloride (PHEN) and controlled-release topiramate (TPM). It thus combines two agents that suppress appetite through complementary and distinct mechanisms (decreased hunger and increased satiety), leading to additive effects on weight loss and allowing for the use of lower doses of the constituent agents.

Phentermine, a synthetic sympathomimetic amine, is an anorectic agent approved by the FDA at a recommended dose of 37.5 mg/day as a short-term adjunct to a weight-loss regimen based on exercise, behavior modification, and caloric restriction (Adipex-P® package insert 2005). Phentermine is the most commonly used anti-obesity drug, with approximately 6.1 million prescriptions written in 2009 (IMS data). The primary mechanism of action appears to be pharmacologically induced anorectic effect via release of norepinephrine in the hypothalamus **(Table 1)**. It is postulated that increased circulating catecholamines may cause appetite suppression by increasing blood leptin concentrations; other studies have demonstrated a correlation between serum leptin concentrations and body weight (Heymsfield 1999; Montague 1997). Phentermine's indication for short-term use in the management of obesity limits its clinical effectiveness as a stand-alone treatment for obesity.

Table 1. *In Vitro* Pharmacological Profile of *d*-Amphetamine and Phentermine on the Release and Re-Uptake of Biogenic Amines

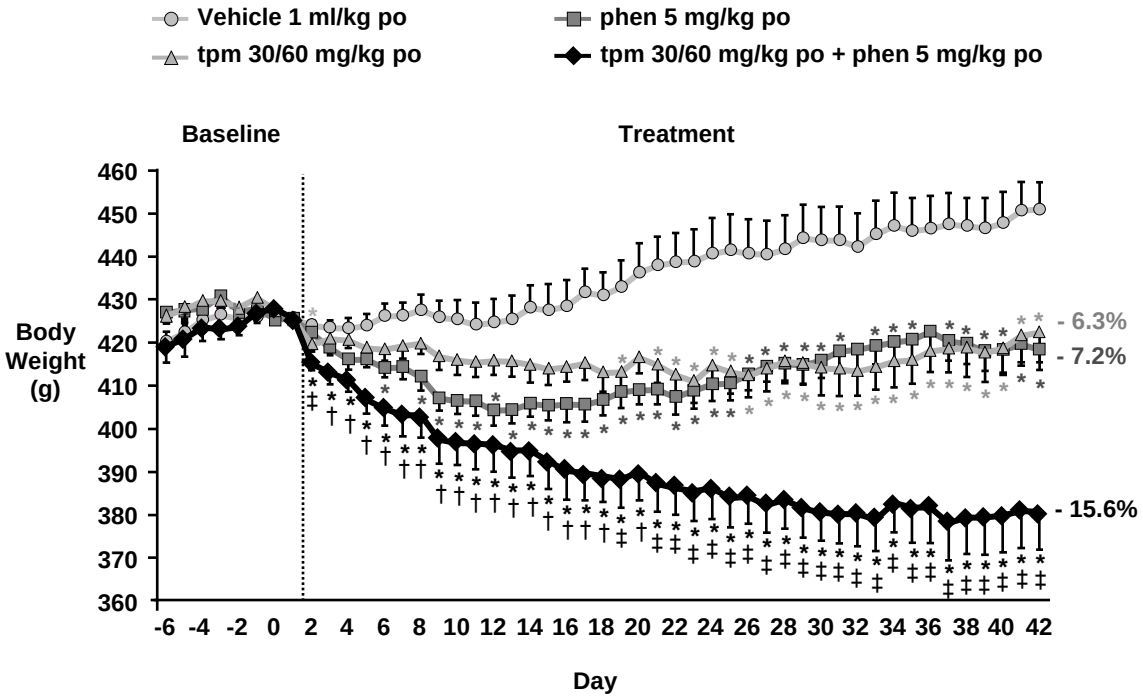
	NE		5-HT		Dopamine		Selectivity for NE
Drug, nM	**Release IC_{50}**	**Uptake K_i**	**Release IC_{50}**	**Uptake K_i**	**Release IC_{50}**	**Uptake K_i**	**NE vs dopamine (ratio of release, IC_{50})**
d-Amphetamine	7.1	39	1765	3830	25	34	3.5
Phentermine	39	244	3511	13900	262	1580	6.7

5-HT=serotonin; IC_{50}=half maximal inhibitory concentration; K_i=inhibition constant; NE=norepinephrine.
Adapted from Rothman RB, et. al. *Synapse.* 2001;39(1):32-41.

Topiramate, a fructose monosaccharide derivative with sulfamate functionality that was originally developed as an antidiabetes compound, is a neurotherapeutic agent approved for treatment of seizure disorders at recommended doses up to 400 mg/day and for migraine headache prophylaxis at recommended doses up to 200 mg/day (Topamax® package insert 2009). More than 9 million prescriptions were written in 2009 for topiramate (IMS data). Several published clinical studies have shown that topiramate monotherapy produces significant weight loss in obese individuals and clinically meaningful improvements in lipid parameters, glycemic control, and blood pressure (Ben-Menachem 2003; Bray 2003; Wilding 2004; Tonstad 2005; Stenlöf 2007). Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety, increased taste aversion (Supuran 2008), increased energy expenditure, and decreased caloric intake (Bray 2003; Richard 2000; Richard 2002; Picard 2000). Topiramate has multiple confirmed molecular mechanisms (modulation of voltage-gated ion channels, potentiation of γ-aminobutyric acid [GABA] inhibition, inhibitory effects on kainate/AMPA type of excitatory glutamate receptors, inhibition of carbonic anhydrase isozymes) that can mediate the pharmacodynamic effects leading to weight loss. A combination of these actions is likely to contribute to the weight loss efficacy of topiramate. Studies conducted in obese rats with phentermine and topiramate administered either alone or in combination indicate an additive (if not synergistic) effect of combination therapy **(Figure 2)** (Jackson 2007).

These nonclinical findings support the proposal that the pharmacological actions of topiramate are distinct and complementary to the actions of phentermine in the management of obesity. The time course of body weight change suggests that phentermine has a faster onset of effect on weight loss compared with topiramate, with which the change is more gradual but sustained throughout the duration of dosing. This complementary, however, sustained weight loss effect is essential for clinically significant and long-term weight loss maintenance in obese subjects.

Figure 2. Primary Pharmacodynamics in Rodent Model of Obesity



Results are adjusted means ± SEM; n=10.
*p<0.05 vs controls.
†p<0.05, topiramate plus phentermine vs topiramate alone.
‡p<0.05, topiramate plus phentermine vs both topiramate and phentermine alone.
phen=commercially available phentermine; po=oral administration; tpm=commercially available topiramate;
Numbers represent % reduction in body weight compared to the control group on Day 42.
Adapted from Jackson HC, et. al. Presented at: Society for Neuroscience Annual Meeting. San Diego, CA; 2007. Poster 629.15/YY18.

While the beneficial effects on co-morbidities are primarily driven by weight reduction, data from nonclinical and clinical studies suggest additional weight-independent effects of topiramate on glycemic parameters, blood pressure, and lipid parameters (Astrup 2004; Stenlöf 2007). Topiramate, however, is associated with dose-limiting side effects, including paresthesia, dizziness, somnolence, insomnia, depression, and difficulty with memory and concentration, which prevent or limit its use as a single agent at the doses necessary to produce significant weight loss or cardiometabolic benefits.

Following the recognition of cardiovascular safety issues associated with fen-phen (fenfluramine and phentermine) treatment, significant effort was directed toward identification of a mechanism to explain the occurrence of the observed cardiac valvulopathy and pulmonary hypertension.

Studies isolated the mechanistic basis of the valvulopathy and pulmonary hypertensive effects to be a specific serotonin receptor (5HT2B) on the heart valves and nonspecific serotonin effects on the lung (Zolkowska 2006**)**. As part of this effort, phentermine was well characterized pharmacologically relative to other anorectic agents (Rothman 1999). The results determined that anorectic agents, such as aminorex, fenfluramine, d-fenfluramine, and chlorphentermine, were responsible for mediating the development of valvular disease and/or pulmonary hypertension through direct (5HT2B affinity) and indirect serotonergic activity. Unlike other anorectic agents, phentermine is inactive at the 5-HT2B receptor (K_i >10000 nM), is not associated with release or reuptake of endogenous serotonin, and has minimal effects on potassium currents (I_K) in pulmonary tissue at 100× above highest efficacious concentrations (Rothman 2000; Reeve 1999). Doppler ECHO measurement during the proof-of-concept study (OB-201) found no evidence of treatment-emergent valvulopathy with the phentermine/topiramate combination.

The proprietary QNEXA formulation utilizes an immediate-release formulation of phentermine and a controlled-release formulation of topiramate in a single capsule. With these formulations, the peak exposure of each drug is separated by 7 to 8 hours, thereby allowing QNEXA to provide phentermine peak coverage near morning/early afternoon and topiramate peak exposure near late afternoon/evening. A single daily dose is also expected to improve overall compliance and ensure morning and late afternoon delivery of active components.

In summary, low doses of the individual agents comprising QNEXA, in conjunction with complementary mechanisms and oppositional pharmacodynamic effects, may provide a safe and effective pharmacotherapy for achieving and maintaining weight loss and for treating weight-related co-morbidities in overweight and obese adults.

2 OVERVIEW OF QNEXA

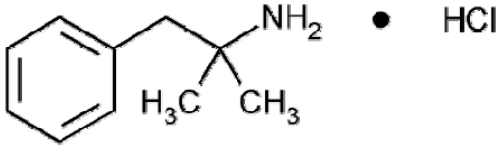
2.1 Chemical Name and Structure

The chemical structures of phentermine hydrochloride and topiramate are shown in **Figure 3**. The chemical name of phentermine is α,α-dimethyl phenethylamine hydrochloride. Phentermine hydrochloride (HCl) has a molecular formula of $C_{10}H_{15}N{\cdot}HCl$ with a molecular weight of 185.7.

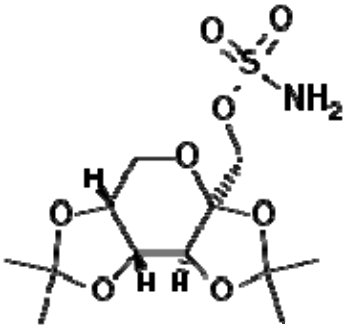
The chemical name of topiramate is 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate. Topiramate has a molecular formula of $C_{12}H_{21}NO_8S$ with a molecular weight of 339.36.

Figure 3. Chemical Structures of Phentermine (A) and Topiramate (B)

A.



B.



2.2 Formulation

QNEXA is hard gelatin capsule containing immediate-release phentermine beads (PHEN) and controlled-release topiramate beads (TPM). QNEXA (PHEN/TPM) capsules are manufactured at 4 dosage strengths, i.e., 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg. The four dosage strengths are graduated to accommodate the need for titration (dose escalation) of each patient up to the prescribed treatment dose. In all clinical studies, phentermine hydrochloride in QNEXA was expressed as the free base.

The PHEN and TPM bead formulations were designed to achieve a time to peak plasma concentration (T_{max}) of 2 to 4 hours and 8 to10 hours, respectively.

2.3 Proposed Indication

QNEXA is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with diet and exercise. QNEXA is recommended for obese patients (BMI ≥30 kg/m^2) or overweight patients (BMI ≥27 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

2.4 Dosage and Administration

The recommendation is to start with QNEXA Low dose (3.75/23 mg) for 14 days, taken once daily (in the morning) with or without food, and then increase to the Mid dose (7.5/46 mg) for 90 days. After 90 days, if weight loss is <3%, treatment should be discontinued. If weight loss is ≥3%, then continue the Mid dose for another 90 days. If weight loss is <10%, or weight loss goal has not been achieved, then titrate to a higher dose. The Top dose (15/92 mg) should be reached by increasing the dose from 7.5/46 mg to 11.25/69 mg for 14 days prior to increasing the dose to 15/92 mg.

In patients with moderate renal impairment (creatinine clearance [CL_{cr}] ≥30 to <50 mL/min) and severe renal impairment (CL_{cr} <30 mL/min), the maximum dose should not exceed 7.5/46 mg (Mid dose).

The respective doses of the QNEXA components were originally chosen based on documented weight loss and tolerability in published studies of the individual agents (Bray 1998; Bray 1999; Bray 2003) and confirmed in the clinical trial program. The results of the proof-of-concept study OB-201 established the target dose and target ratio and demonstrated that the phentermine/topiramate combination produced a magnitude of weight loss (~10%) that exceeded current pharmacotherapies, exceeded either drug as monotherapy, and exceeded FDA criteria for approval of weight-loss agents (Food and Drug Administration 2007). The QNEXA Mid and Low doses were studied in Phase 3 with the intent to identify a minimally efficacious dose and provide a greater understanding of the dose-response properties of the drug. The availability of various doses of QNEXA will provide dosing flexibility for individual needs and the needs of different patient populations.

3 REGULATORY AND DEVELOPMENT HISTORY

3.1 Regulatory History

The New Drug Application (NDA) for QNEXA was submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The FDA Draft Guidance for Industry – Applications

Covered by Section 505(b)(2) – FDA Guidance defines a 505(b)(2) application as "one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." Because the active components of QNEXA, phentermine hydrochloride and topiramate, have already been approved by the FDA, the NDA for QNEXA relies on the FDA's previous determination of safety for these products in addition to the clinical studies conducted by VIVUS to support the efficacy and safety of QNEXA for the treatment of obesity.

The NDA describes a comprehensive clinical development program conducted by VIVUS to support the efficacy and safety of QNEXA for the treatment of obesity. Important aspects of the development program, including the number of subjects treated, the populations evaluated, the duration and design of the studies providing pivotal efficacy and safety data, and the endpoints evaluated in these studies were agreed upon by VIVUS and the FDA Division of Metabolism and Endocrinology Products through a Special Protocol Assessment. An independent Data Safety Monitoring Board was utilized throughout the Phase 3 program to oversee safety.

3.2 Nonclinical Overview

The available nonclinical pharmacology data for phentermine and topiramate as single agents supports the rationale of a fixed-dose combination product for the treatment of obesity.

The toxicity profile of the phentermine/topiramate combination is consistent with that of phentermine and topiramate as single agents. No unique toxicities or synergistic effects were noted in animals when phentermine and topiramate were administered in combination to either rats or dogs for 13 weeks. Neither topiramate nor phentermine pose a carcinogenic or genotoxic risk.

Both topiramate and phentermine are currently labeled as Pregnancy Category C. QNEXA has not demonstrated selective developmental toxicity, including teratogenicity, at ~6-fold and ~13-fold above the recommended human dose (RHD = QNEXA Mid dose), in rats and rabbits, respectively. Because weight loss during pregnancy is not desirable, QNEXA (or any other

weight loss medication) is not recommended for use in patients who are pregnant or plan to become pregnant. Adequate contraception should be used in women of child-bearing potential for the prevention of unintended pregnancy, as weight-loss may improve fertility.

Taken together, the nonclinical pharmacology, pharmacokinetics and toxicology data submitted in the QNEXA NDA support the use of the phentermine/topiramate combination product for the proposed chronic treatment of obesity, including weight loss and management of weight loss.

3.3 Clinical Development Program

The QNEXA clinical development program included three Phase 3 studies (OB-302 and OB-303, both 56-week pivotal trials; and OB-301, a 28-week confirmatory study) that evaluated the efficacy and safety of three fixed-dose combinations of QNEXA for the treatment of obesity in individuals with and without weight-related co-morbidities. The three doses studied were QNEXA Low dose, 3.75/23 mg, QNEXA Mid or recommended dose, 7.5/46 mg, and QNEXA Top dose, 15/92 mg.

The QNEXA clinical development program also included four Phase 2 studies (OB-201, OB-202, DM-230, DM-231) considered supportive of the indication for the treatment of obesity. Studies OB-201 and OB-202 were proof-of-concept studies that compared the effects of concomitant QNEXA versus monotherapy with phentermine, topiramate, or placebo. In addition, the data from 10 Phase 1 studies were provided as part of the overall safety database.

The number of subjects and dosage strengths evaluated in the QNEXA clinical development program are summarized in **Table 2**.

Throughout the Phase 2 and Phase 3 program, subjects randomized into these studies were advised to initiate a lifestyle change program using the LEARN® Program for Weight Management (see **Appendix 7**). The 16-week LEARN program is designed to aid in weight management by providing tools to facilitate lifestyle, attitude, relationship, nutrition, and exercise changes. Patients were provided with a LEARN manual, and site personnel were encouraged to discuss these material with patients at their regularly scheduled visits.

Table 2. Summary of Clinical Exposure in Trials of QNEXA Combination Drug

Study Code	Dosage of QNEXA				Total QNEXA	Placebo	Total
	Low	Mid[a]	Top[b]	Other			
Phase 1 studies							
OB-102		16	29		45		45
OB-103			32		32		65
OB-105			24		24		24
OB-106			33		33		33
OB-107			20		20		20
OB-108			20		20		20
OB-109	88	70		72[c]	230		230
OB-110			14		14[d]		14
OB-118		56		56[e]	56	56	112
Phase 1 total					474	56	563
Phase 2 studies							
OB-201			50		50[f]	50	200
OB-202			105		105	105	210
DM-230[g]			75		75	55	130
OB-205		45	45		45	45	45
Phase 2 Total					200	255	455
Phase 3 studies							
OB-301		107	108		215[h]	109	756
OB-302	241	0	512		753	514	1267
OB-303		498	995		1493	994	2487
Phase 3 total					2461	1617	4510
Total	329	792	1987	128	3135	1873	5528

a. Includes doses of 7.5/50 mg.
b. Includes doses of 15/100 mg.
c. Subjects received a single dose of 11.25/69 mg.
d. Additional 15 subject received single-agent phentermine and 12 subject received single-agent topiramate.
e. Supratherapeutic dose of 22.5/138 mg.
f. Additional 100 subjects were randomized to treatment with single-agent phentermine or single-agent topiramate
g. DM-230 and DM-231 were extension studies in which some subjects from OB-202 and DM-230 elected to continue treatment and thus, these subjects were excluded from total calculations.
h. Additional 432 subjects were randomized to treatment with single-agent phentermine or single-agent topiramate.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

3.4 Overview of Clinical Pharmacology

The clinical pharmacology of phentermine and topiramate is well established, as evidenced by the literature and the use of these compounds in marketed products—50 years for phentermine and more than 14 years for topiramate. Ten Phase 1 studies have been completed for the QNEXA development program. Additionally, population pharmacokinetic (popPK) and popPK/pharmacodynamic (PD) modeling were performed by Pharsight (Mountain View, California, USA) for VIVUS to provide further insight into selected clinical pharmacology objectives.

3.4.1 Pharmacokinetic Profile

The pharmacokinetic (PK) profile of phentermine and topiramate are characterized by good oral absorption, large distribution with low plasma protein binding, low cytochrome P450 (CYP) and/or monoamine oxidase (MAO) metabolism, and primarily eliminated via urine resulting in low inter-subject variability. The peak plasma concentration (C_{max}) was 29% lower and the time to peak plasma concentration (T_{max}) was 7 hours longer for the controlled-release QNEXA Top dose than for immediate-release topiramate (Topamax 100 mg). The areas under the concentration-time curves (AUC) for the controlled-release and immediate-release formulations were equivalent.

Single doses of QNEXA Mid dose administered to healthy obese subjects resulted in a C_{max} for phentermine of 23.5 ng/mL between 2 and 10 hours post-dose (median T_{max}, 6 hours) and a C_{max} for topiramate of 362 ng/mL between 7 and 16 hours post-dose (median T_{max}, 10 hours). The AUC from time zero to infinity ($AUC_{0\text{-}inf}$) and apparent terminal half-life for phentermine were 867 ng·h/mL and 20 hours, respectively. The $AUC_{0\text{-}inf}$ and apparent terminal half-life for topiramate were 30,100 ng·h/mL and 65 hours, respectively. The plasma AUC and C_{max} of phentermine and topiramate increased approximately 2.5- to 2.9-fold and 3.7- to 5.2-fold, respectively, with multiple dosing. Plasma AUC of phentermine and topiramate increased in an approximately dose-proportional manner. Co-administration of a high-fat meal with QNEXA had no effect on the pharmacokinetics of phentermine and topiramate. QNEXA may be administered with or without food.

The rate of phentermine excretion is increased in acidic urine and decreases in alkaline urine. Compounds that increase the urine pH, such as carbonic anhydrase inhibitors, are expected to decrease phentermine excretion. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of phentermine was CYP3A4.

Population PK analyses showed a positive correlation between body weight and apparent volumes of distribution and between CL_{cr} and plasma clearances of phentermine and topiramate. The PK profile of QNEXA was similar in healthy obese subjects and in subjects with type 2 diabetes. No relationship was observed between PK parameters and age, BMI, race, or sex for either drug. Population PK/PD modeling indicated that topiramate and phentermine AUC correlates with weight loss. The effect of phentermine and topiramate in QNEXA on maximal percent weight loss appeared to be additive. The maximum effect on weight loss in female subjects was found to be slightly higher than that observed in male subjects. The maximum effect on weight loss in subjects without diabetes was higher than that observed in subjects with diabetes. Treatment with topiramate, as a monotherapy or in the PHEN/TPM combination product, resulted in statistically significant and clinically meaningful reductions in systolic blood pressure and heart rate, thereby mitigating the potential side effects of phentermine. Subjects with a higher baseline BMI, who were treated with QNEXA Top dose, demonstrated greater and progressive absolute weight loss as compared with subjects with lower BMI.

Details of the ten Phase I studies are provided in **Table 46** in **Appendix 3**.

3.4.2 Assessment of Drug-Drug Interactions

In Vitro

Topiramate and phentermine do not inhibit CYP isozymes. Phentermine is neither a substrate nor an inhibitor of MAOs. Topiramate is a mild inducer of CYP3A4 isozyme; however, phentermine is not an inducer of CYP isozymes. Topiramate and phentermine are neither substrates nor inhibitors of human P-glycoprotein. Topiramate is a weak inhibitor of human organic anion and cation transporters. Based on these results, topiramate and phentermine are considered unlikely to cause interactions with other drugs that utilize these pathways.

Topiramate and phentermine have low plasma protein binding. Therefore, the propensity of topiramate and phentermine to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

Effect of QNEXA on Oral Contraceptives

Co-administration of QNEXA Top dose with a single oral contraceptive containing 35 µg ethinyl estradiol and 1 mg norethindrone decreased the $AUC_{0\text{-}inf}$ of ethinyl estradiol by 16% and increased the C_{max} and $AUC_{0\text{-}inf}$ of norethindrone by 22% and 16%, respectively. The possibility of decreased contraceptive efficacy should be considered in patients taking QNEXA concomitantly with oral contraceptives containing estrogen.

Effect of QNEXA on Metformin

Co-administration of QNEXA Top dose with multiple doses of metformin 500 mg twice daily (BID) to healthy obese subjects increased the C_{max} and $AUC_{0\text{-}\tau}$ of metformin by approximately 16% and 23%, respectively. No dosage adjustment of metformin or QNEXA is recommended.

Effect of QNEXA on Sitagliptin

Co-administration of QNEXA Top dose with sitagliptin did not affect the PK of sitagliptin in healthy obese subjects.

Effect of Metformin, Sitagliptin, and Probenecid on QNEXA

Co-administration of multiple doses of metformin BID, multiple doses of sitagliptin once daily (QD), or a single dose of probenecid with QNEXA did not affect the steady-state C_{max} and $AUC_{0\text{-}\tau}$ of either phentermine or topiramate.

Effect of Statins, Antihypertensive Agents, SSRIs, and Oral Diabetic Medications on QNEXA

Population PK/PD analyses of Phase 2 and Phase 3 study data indicated PK parameters of phentermine or topiramate were not affected in subjects receiving QNEXA concomitantly with

statins, antihypertensive medications, antidiabetic medications (metformin, sulfonylureas, and thiazolidinedione), or selective serotonin reuptake inhibitors.

3.4.3 Special Populations

In subjects with mild or moderate hepatic impairment, exposure to phentermine was 37% and 60% higher compared with normal subjects. Dose escalation above the recommended dose of 7.5/46 mg may be considered in light of the degree of hepatic impairment and therapeutic benefit of the higher dose.

The phentermine and topiramate components of QNEXA are primarily cleared by renal excretion, and exposure is increased in patients with moderate to severe renal impairment. In subjects with moderate (CL_{cr} ≥30 to <50 mL/min) or severe (CL_{cr} <30 mL/min) renal impairment the maximum dose should not exceed 7.5/46 mg.

3.4.4 Effect on Cardiac Electrophysiology

Study OB-118 was a double-blind, randomized, placebo- and active-controlled (moxifloxacin), thorough QT/QTc study that evaluated the effects of the intended therapeutic dose (QNEXA Mid) and a supratherapeutic dose (QNEXA 22.5/138 mg) on the QT/QTc interval in healthy volunteers. Moxifloxacin used as a positive control met the assay sensitivity requirement, thus validating the results of this thorough QT/QTc study.

The results from this study, demonstrated by analyses of both central tendency and outliers, indicate that QNEXA has no effect on cardiac repolarization of clinical or regulatory concern. Specifically, the point estimate of change in QTc interval was <5 msec at all post-dose time points in both the therapeutic and the supra-therapeutic dose groups, and the upper limit of the one-sided 95% confidence interval was <10 msec at all time points.

3.4.1 Effects on Psychomotor Function

Study OB-205 evaluated the psychomotor effects of QNEXA compared with placebo in healthy overweight and obese adults. This study included alcohol as a positive control. Subjects were assigned randomly to receive 1 day of treatment with active comparator (alcohol mixed with fruit

juice) or placebo (fruit juice) for the first period of the study, and to the order in which they would receive each of two treatments for the latter two periods of the study: QNEXA capsules or placebo daily for 4 weeks, with a 1-week washout between treatment periods, and a 1-week follow-up at the end of the study. Study drug was administered at the center on days when psychomotor tests were performed. Results indicated that QNEXA does not induce psychomotor deficits compared with placebo.

4 QNEXA CLINICAL DEVELOPMENT AND OVERVIEW OF EFFICACY

Key efficacy findings from the QNEXA clinical development program include the following points:

- Subjects treated with all three doses of QNEXA experienced significantly greater percentage and categorical weight loss from baseline compared with subjects treated with placebo. Weight loss from baseline observed at Week 28 was sustained through Week 56.

- A significantly higher proportion of subjects treated with QNEXA experienced a greater than 5%, 10%, or 15% weight loss from baseline compared with subjects treated with the individual components alone or placebo.

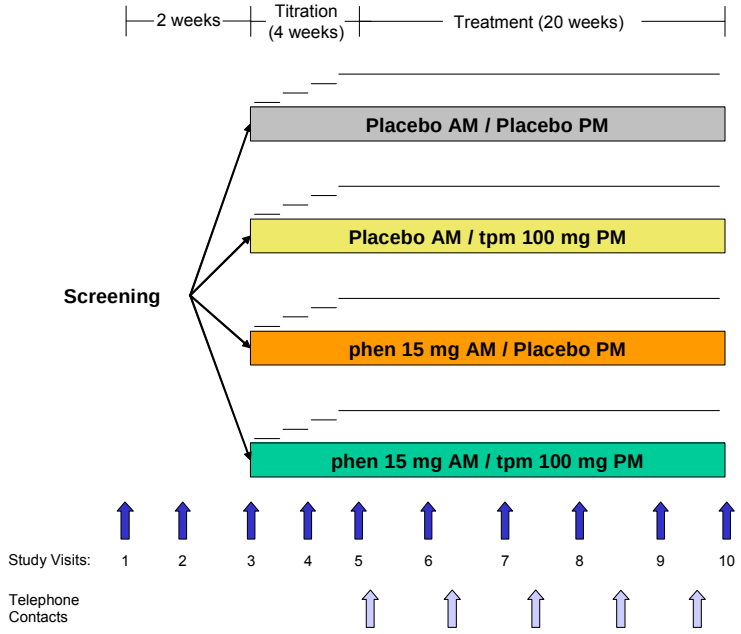
- Dose-related improvements in obesity-related co-morbidities, such as blood pressure, blood lipids, and diabetes markers, were observed across all studies and subjects (intent-to-treat–last observation carried forward [ITT-LOCF]); however, improvements of the greatest magnitude were observed in pivotal study OB-303, which included overweight and obese subjects who had ≥2 co-morbidities at baseline.

- Reductions of concomitant medications to treat co-morbidities were observed in QNEXA-treated subjects experiencing improvements in obesity-related co-morbidities.

4.1 Proof-of-Concept Study (OB-201)

OB-201 was a Phase 2, randomized, double-blind, placebo-controlled, single-center study of obese adults that compared weight loss from baseline in subjects treated with placebo, single-agent phentermine and topiramate components, or combination phentermine and topiramate, after 24 weeks (**Figure 4)**. The study population consisted of 200 adult subjects ≤60 years of age with a BMI ≥30 and ≤50 kg/m^2. Eligible subjects were randomized to receive daily treatment with the combination of phentermine 15 mg and topiramate 100 mg administered as phentermine HCl in the morning and topiramate in the evening; phentermine 15 mg alone; topiramate 100 mg alone; or placebo. The primary efficacy endpoint was percent weight loss.

Figure 4. OB-201 Study Schematic



Note: Subjects were given maintenance dose equivalents of anhydrous dextrose for the AM dose (tpm monotherapy), the PM dose (phen monotherapy), or the AM and PM dose (placebo therapy). At the end of the 20-week maintenance treatment period, there was a 4-day dose discontinuation period.
phen=commercially available phentermine; tpm=commercially available topiramate.

Study Population: Demographic and baseline characteristics were similar for all subjects randomized across each population group. Females comprised 79.5%, and males comprised 20.5% of the ITT population. Caucasians (103 [51.5%]) and African Americans (91 [45.5%]) were distributed with roughly equal representation across all treatment groups. The mean age of subjects participating in this study was 40.2 years and the mean weight was 107 kg. The mean BMI was 38.6 kg/m^2.

Inclusion/Exclusion Criteria: Subjects were included if they had met the following criteria: (1) age 18 to 60 years; (2) BMI of ≥30 to ≤50 kg/m^2 (National Institute of Health [NIH] criteria for obesity, BMI ≥30 kg/m^2); and (3) otherwise healthy as determined by the principal investigator.

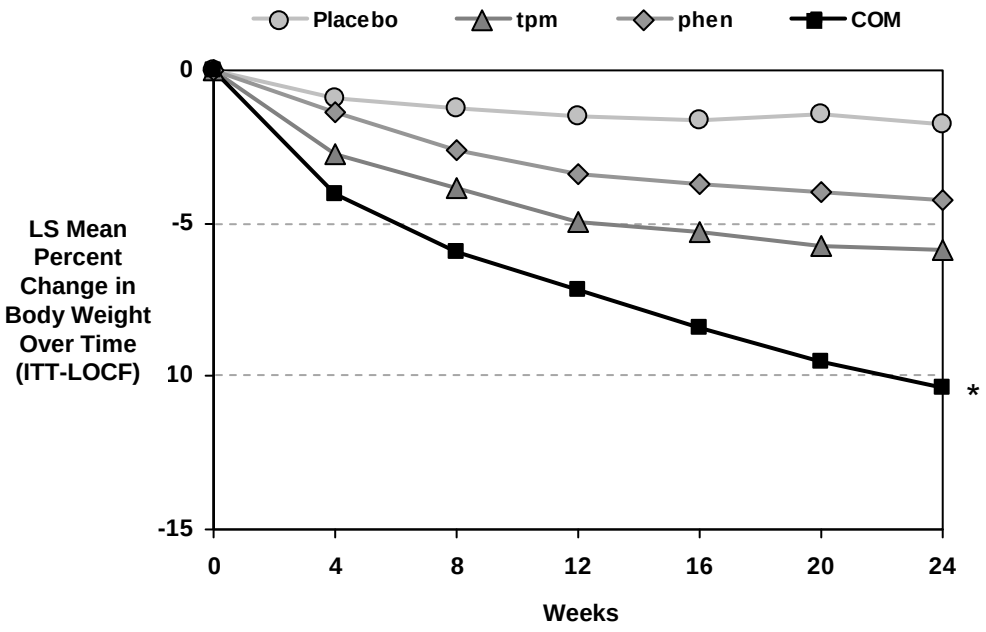
Subjects were excluded from the study if they had (1) obesity of an endocrine origin; (2) significant cardiovascular disease; (3) hepatic or renal disease; (4) diabetes; (5) thyroid disease; (6) current major psychiatric disorder, or alcohol or drug abuse; (7) glaucoma; (8) pregnancy; (9)

uncontrolled hypertension; (10) epilepsy; (11) history of renal calculi; or (12) known history of stroke or valvular heart disease.

In total, 158 subjects (79.0%) completed the study to Week 24, and 42 subjects (21.0%) discontinued from the study. Among subjects treated with placebo, phentermine, topiramate, or combination therapy, 38%, 24%, 14%, 8%, and, respectively, discontinued from the trial. The most common reasons for discontinuation were loss to follow-up (7.5%) and AEs (5.0%).

Treatment with the combination of phentermine 15 mg and topiramate 100 mg resulted in a least-squares (LS) mean percent weight loss from baseline of 10.7%, which was significantly greater than weight loss achieved with phentermine 15 mg monotherapy (4.6%), topiramate 100 mg monotherapy (6.3%), and placebo (2.1%) after 24 weeks **(Figure 5)**.

Figure 5. Percent Weight Loss From Baseline Over Time — Study OB-201 (ITT-LOCF Set)



*p<0.0001 vs placebo and monotherapy.
COM=combination of phentermine and topiramate; ITT-LOCF=intent-to-treat–last observation carried forward; phen=commercially available phentermine; tpm=commercially available topiramate.

Treatment with phentermine 15 mg and topiramate 100 mg resulted in a significantly higher proportion of subjects (82.0%, 50.0%, 20.0%) with ≥5%, ≥10%, and ≥15% weight loss from baseline, respectively, compared with either monotherapy (phentermine, 38.0%, 14.0%, 4.0%;

topiramate, 50.0%, 16.0%, 4.0%) or placebo (14.0%, 8.0%, 0.0%). The observed treatment effect on categorical weight loss was greater than additive for the combination compared with monotherapy. The mean change in waist circumference from baseline to Week 24 was -4.8 cm for the placebo group, -6.0 cm for the phentermine 15 mg group, -7.6 cm for the topiramate 100 mg group, and -12.1 cm for the phentermine/topiramate 15/100 mg group. (All analyses were based on the ITT-LOCF population.)

The results of this study demonstrated that the combination of phentermine and topiramate provided an additive effect on weight loss compared with either agent as monotherapy, and also established a target dose for further assessment in the Phase 3 clinical study program, because at least 50% of subjects on combination therapy achieved the ≥10% categorical weight loss threshold.

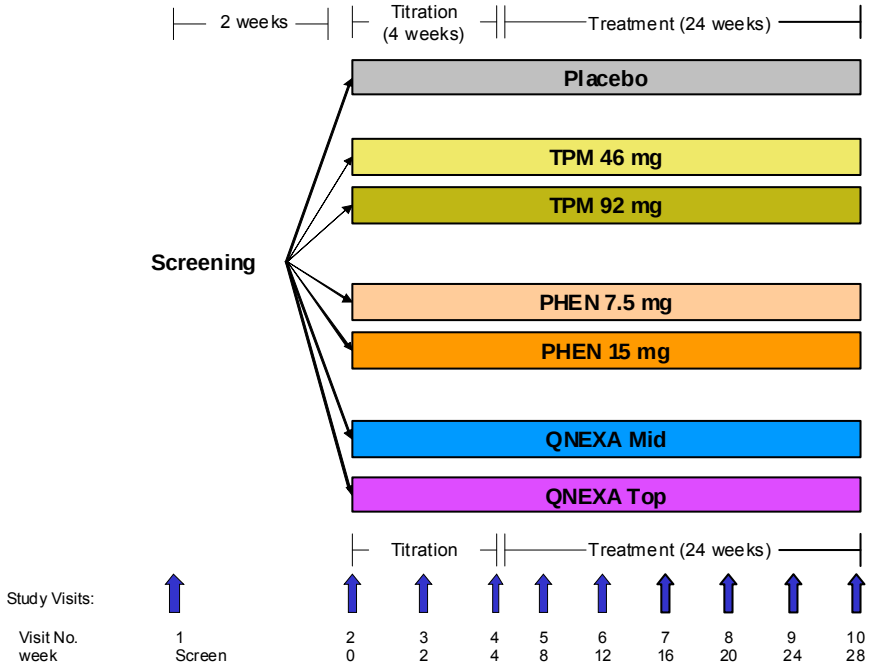
Based on results from this Phase 2 proof-of-concept study, the QNEXA Phase 3 clinical trial program was initiated. The following section, "Phase 3 Trial Descriptions," outlines the study design, baseline demographics, and subject disposition for each of the QNEXA Phase 3 trials. Efficacy results for each trial and an integrated analysis of efficacy across trials are presented in **Section 4.3**, "Results and Integrated Efficacy Summary Across the QNEXA Phase 3 Program."

4.2 Phase 3 Trial Descriptions

4.2.1 Six-Month Factorial Study (OB-301)

OB-301 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter factorial trial that compared weight loss from baseline at 28 weeks in subjects treated with placebo, QNEXA Mid dose, Top dose, and the respective single-agent phentermine and topiramate components at doses corresponding to the combination, in obese subjects after 28 weeks of treatment. The study schema is diagrammed in **Figure 6**.

Figure 6. OB-301 Study Schematic



PHEN=proprietary capsule formulation of phentermine HCl; QNEXA=fixed-dose combination of phentermine and topiramate; TPM=proprietary capsule formulation of topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.2.1.1 OB-301 Study Population and Inclusion/Exclusion Criteria

The study population consisted of adult subjects ≤70 years of age with a BMI ≥30 and ≤45 kg/m^2. Most subjects were female (79.2%) and Caucasian (79.2%). The TPM 46 mg group, PHEN 15 mg group, and PHEN/TPM 15/92 mg group had a higher proportion of Caucasian subjects and lower proportion of African subjects than the other treatment groups. The mean age of subjects was 45.6 years. At baseline, mean weight was 101.3 kg, mean BMI was 36.3 kg/m^2, and mean waist circumference was 111.1 cm. At baseline, mean systolic blood pressure (SBP) was 122.1 mm Hg and mean diastolic blood pressure (DBP) was 79.0 mm Hg. With the exception of race, the treatment groups were comparable with respect to demographic and baseline characteristics. No statistically significant differences were observed among the treatment groups in mean weight, BMI, and waist circumference at baseline.

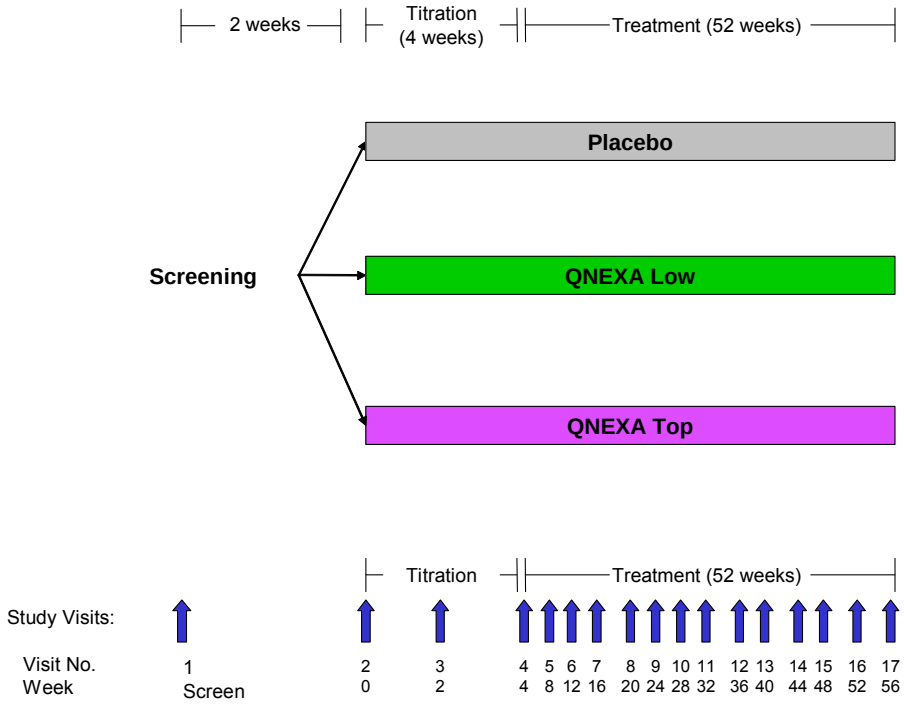
Diagnosis and Main Criteria for Inclusion: The study population included adult subjects ≤70 years of age with a BMI ≥30 kg/m^2 and ≤45 kg/m^2.

A total of 756 eligible subjects were randomly assigned to receive daily treatment with placebo (n=109), phentermine 15 mg (n=108), phentermine 7.5 mg (n=109), topiramate 92 mg (n=107), topiramate 46 mg (n=108), QNEXA Mid dose, 7.5/46 mg capsules (n=107), or QNEXA Top dose, 15/92 mg capsules (n=108). Randomization was stratified by sex to ensure a similar distribution of male and female subjects across the treatment groups. For efficacy results see **Section 4.3**.

4.2.2 Pivotal Study in Severely Obese Subjects (OB-302)

Study OB-302 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial with obese adults that compared weight loss from baseline in subjects treated with placebo, QNEXA Low dose, or Top dose after 56 weeks of treatment. The study population consisted of adult subjects ≤70 years of age with a BMI ≥35 kg/m^2 (no upper limit). Subjects with type 2 diabetes, hypertension (blood pressure >140/90 mm Hg or treatment with >2 antihypertensive medications), and hypertriglyceridemia (triglycerides [TG] >200 mg/dL or treatment with ≥2 lipid-lowering medications) were excluded from participation in this study. Eligible subjects were randomized 2:1:2 to receive daily treatment with placebo, QNEXA Low dose, 3.75/23 mg, or QNEXA Top dose, 15/92 mg capsules **(Figure 7)**. Randomization was stratified by sex to ensure a similar distribution of male and female subjects across the treatment groups. The co-primary endpoints were percent and categorical weight loss at study end (Week 56). For efficacy results see **Section 4.3**.

Figure 7. OB-302 Study Schematic



QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Top, 15/92 mg.

4.2.2.1 OB-302 Study Population and Inclusion/Exclusion Criteria

In study OB-302 most subjects were female (82.9%) and Caucasian (80.0%). The mean age of subjects was 42.6 years. At baseline, mean weight was 116.1 kg, mean BMI was 42.1 kg/m^2, and mean waist circumference was 120.5 cm. At baseline, mean SBP was 122.0 mm Hg and mean DBP was 77.4 mm Hg. The treatment groups were comparable with respect to demographic and baseline characteristics. No statistically significant differences among the treatment groups in mean weight, BMI, waist circumference, blood pressure, lipids, and fasting serum glucose at baseline were observed.

Diagnosis and Main Criteria for Inclusion: The study population included adult subjects ≤70 years of age with a BMI ≥35 kg/m^2 (no upper limit on BMI inclusion criterion). Subjects were required to have TG ≤200 mg/dL with treatment of 0 or 1 lipid-lowering medication, blood pressure ≤140/90 mm Hg with treatment of 0 to 2 antihypertensive medications, and fasting

serum glucose ≤110 mg/dL for inclusion. Subjects with type 2 diabetes by history (or as confirmed by fasting serum glucose ≥126 mg/dL or history of antidiabetic medication use) were excluded from participation.

4.2.2.2 Demographics at Baseline and Subject Disposition

In study OB 302 subjects were balanced across treatment groups with respect to baseline demographic characteristics and obesity-related co-morbidities (**Table 3).** A total of 1267 subjects were assigned randomly to treatment **(Figure 8)**. In total, 759 (59.9%) subjects completed all study visits, and 508 (40.1%) subjects discontinued from the study. The percentages of subjects who completed the study were 52.9% in the placebo group, 61.0% in the QNEXA Low dose group, and 66.4% in the Top dose group. Of the 1267 randomized subjects, 680 (53.7%) subjects completed all study visits on study drug, and 584 (46.1%) subjects discontinued study drug. The percentages of subjects who completed the study on study drug were 58.8% in the QNEXA Top group, 57.3% in the QNEXA Low group and 46.9% in the placebo group. A total of 79 subjects who discontinued study drug completed follow-up visits.

Table 3 provides a summary of demographics and baseline characteristics of subjects enrolled in study OB-302.

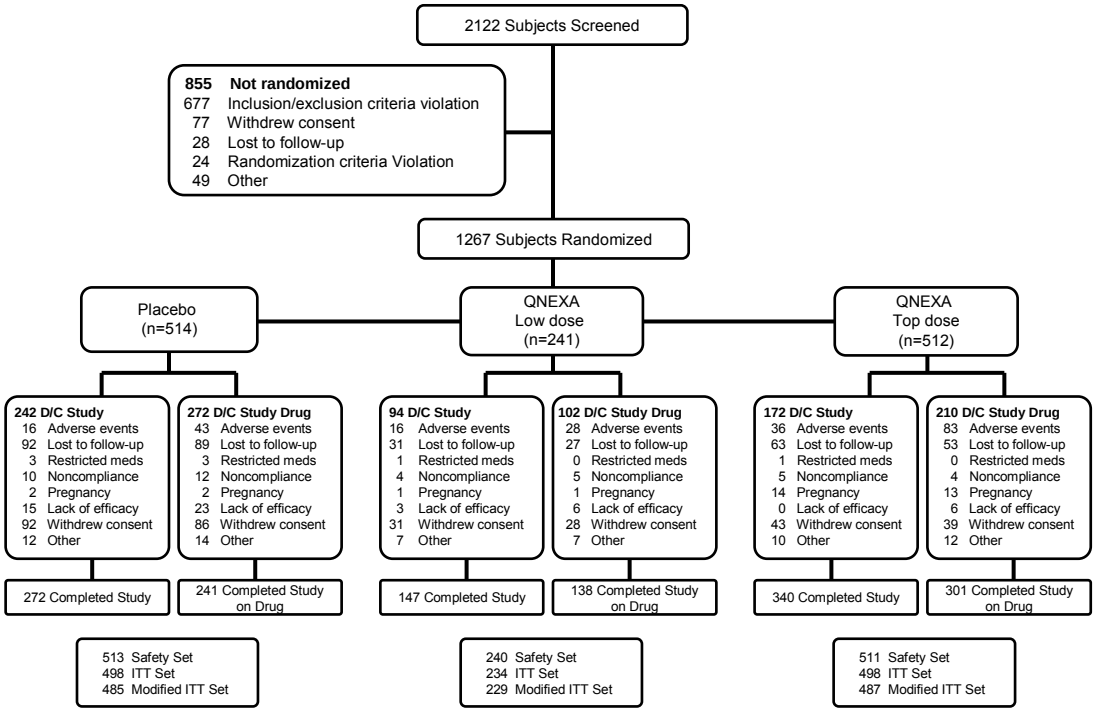
Table 3. Demographic and Baseline Characteristics (Randomized Set, Study OB-302)

	Placebo (N=514)	QNEXA Low (N=241)	QNEXA Top (N=512)	Total (N=1267)
Age, years				
N	514	241	512	1267
Mean (SD)	43.0 (11.76)	43.0 (10.96)	41.9 (12.21)	42.6 (11.80)
Sex, n (%)				
Female	425 (82.7)	201 (83.4)	424 (82.8)	1050 (82.9)
Male	89 (17.3)	40 (16.6)	88 (17.2)	217 (17.1)
Race, n (%)				
Caucasian	413 (80.4)	192 (79.7)	408 (79.7)	1013 (80.0)
African American	93 (18.1)	39 (16.2)	93 (18.2)	225 (17.8)
American Indian or Alaskan native	6 (1.2)	2 (0.8)	7 (1.4)	15 (1.2)
Asian	3 (0.6)	2 (0.8)	1 (0.2)	6 (0.5)
Native Hawaiian or other Pacific Islander	2 (0.4)	1 (0.4)	2 (0.4)	5 (0.4)
Other	4 (0.8)	5 (2.1)	7 (1.4)	16 (1.3)
Weight, kg				
N	513	240	511	1264
Mean (SD)	115.8 (21.46)	118.5 (21.85)	115.2 (20.66)	116.1 (21.23)
Height, cm				
N	513	240	511	1264
Mean (SD)	165.9 (9.11)	166.6 (8.57)	165.6 (8.62)	165.9 (8.81)
Body mass index, kg/m^2				
N	513	240	511	1264
Mean (SD)	42.0 (6.15)	42.6 (6.50)	41.9 (6.04)	42.1 (6.18)
Waist circumference, cm				
N	513	240	511	1264
Mean (SD)	120.5 (13.92)	121.7 (15.15)	120.1 (14.63)	120.5 (14.45)
Low-density lipoprotein cholesterol, mg/dL				
N	512	240	511	1263
Mean (SD)	121.3 (32.02)	122.5 (32.96)	119.8 (30.06)	121.0 (31.42)
High-density lipoprotein cholesterol, mg/dL				
N	513	240	511	1264
Mean (SD)	49.5 (13.09)	50.2 (11.20)	49.8 (11.72)	49.8 (12.19)
Total cholesterol, mg/dL				
N	513	240	511	1264
Mean (SD)	194.7 (36.36)	196.1 (36.08)	192.5 (33.77)	194.1 (35.28)
Triglycerides, mg/dL				
N	513	240	511	1264
Mean (SD)	118.8 (39.20)	116.7 (40.12)	114.0 (37.24)	116.5 (38.63)
Fasting serum glucose, mg/dL				
N	510	240	511	1261
Mean (SD)	93.0 (8.70)	93.8 (9.11)	93.0 (9.47)	93.2 (9.10)
Systolic blood pressure, mm Hg				
N	513	240	511	1264
Mean (SD)	121.8 (11.45)	122.5 (11.08)	122.0 (11.58)	122.0 (11.43)
Diastolic blood pressure, mm Hg				
N	513	240	511	1264
Mean (SD)	77.2 (7.85)	77.8 (7.46)	77.4 (7.69)	77.4 (7.71)

Hypertension				
n (%)	1 (0.2)	1 (0.4)	0 (0.0)	2 (0.2)
Dyslipidemia				
n (%)	107 (20.9)	43 (17.9)	94 (18.4)	244 (19.3)
Diabetes mellitus				
n (%)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
History of depression				
n (%)	81 (15.8)	47 (19.6)	74 (14.5)	202 (16.0)
History of major depression				
n (%)	0 (0.0)	1 (0.4)	2 (0.4)	3 (0.2)

QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Low, 3.75/23 mg; QNEXA Top, 15/92 mg.

Figure 8. Subject Disposition in Study OB-302



Subjects may be counted in both discontinuation sections.
D/C=discontinued; ITT=intent-to-treat; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23mg; QNEXA Top, 15/92 mg.

4.2.3 Pivotal Study in Overweight and Obese Subjects With Co-Morbidities (OB-303)

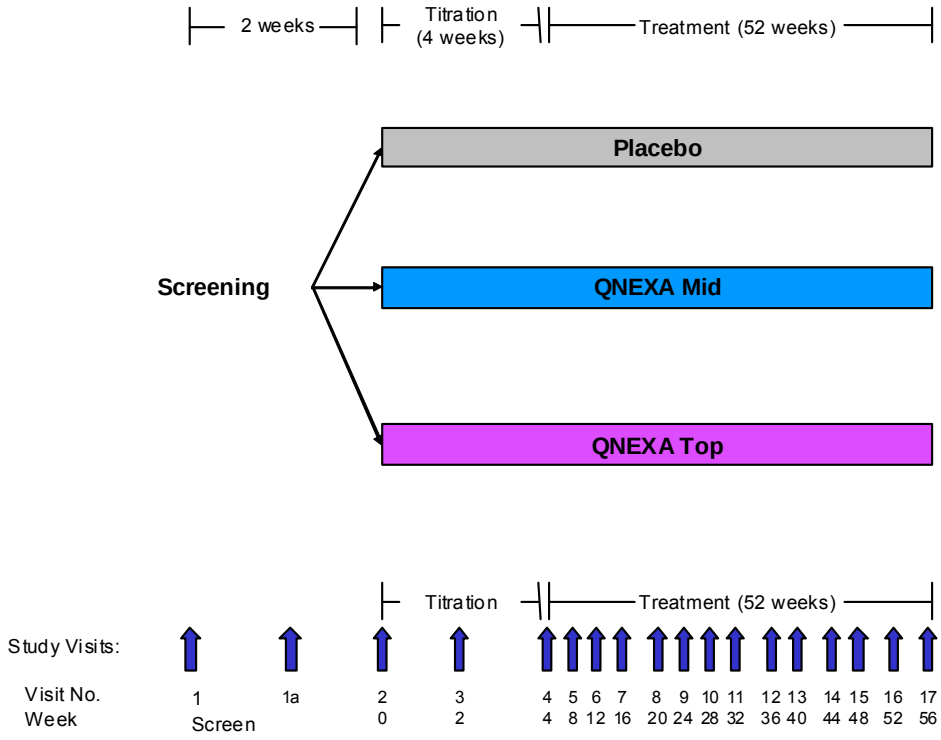
Study OB-303, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial, compared weight loss from baseline at 56 weeks in overweight or obese subjects with weight-

related co-morbidities who were treated with QNEXA Top (15/92 mg), QNEXA Mid (7.5/46 mg), or placebo. The study population consisted of adult subjects ≤70 years of age with a BMI ≥27 and ≤45 kg/m^2 and with two or more of the following weight-related co-morbid conditions:

- Elevated blood pressure, defined as SBP ≥140 and ≤160 mm Hg (≥130 and ≤160 mm Hg in subjects with diabetes), DBP ≥90 and ≤100 mm Hg (≥85 and ≤100 mm Hg in subjects with diabetes), or requirement for ≥2 antihypertensive medications
- Elevated TG, defined as TG ≥200 and ≤400 mg/dL or requirement for ≥2 lipid-lowering medications
- Fasting blood glucose >100 mg/dL, glucose >140 mg/dL at 2 hours post-glucose challenge during oral glucose tolerance testing, or a diagnosis of type 2 diabetes managed with lifestyle measures or metformin monotherapy
- Waist circumference ≥102 cm for men and ≥88 cm for women

Eligible subjects were randomly assigned 2:1:2 to receive daily treatment with placebo, QNEXA Mid dose (7.5/46 mg), or QNEXA Top dose (15/92 mg) **(Figure 9)**. The groups were balanced for sex and diabetic status; the Top-dose and placebo treatment groups had twice as many subjects as the Mid-dose group. The co-primary endpoint was percent weight loss and the percentage of subjects achieving 5% weight loss at study end (Week 56). For efficacy results see **Section 4.3**.

Figure 9. OB-303 Study Schematic



QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.2.3.1 OB-303 Study Population and Inclusion/Exclusion Criteria

Most subjects were female (69.8%) and Caucasian (86.0%). The mean age of subjects was 51.1 years. At baseline, mean weight was 103.1 kg, mean BMI was 36.6 kg/m^2, and mean waist circumference was 113.2 cm. At baseline, mean SBP was 128.4 mm Hg and mean DBP was 80.6 mm Hg. At baseline, mean low-density lipoprotein cholesterol (LDL-C) was 123.1 mg/dL, mean high-density lipoprotein cholesterol (HDL-C) was 48.9 mg/dL, mean total cholesterol (TC) was 204.5 mg/dL, and mean TG was 162.5 mg/dL. At baseline, mean hemoglobin A_{1c} (HbA_{1c}) was 5.9% and mean fasting serum glucose was 106.1 mg/dL. The treatment groups were comparable with respect to demographic and baseline characteristics. No statistically significant differences among the treatment groups in mean weight, BMI, waist circumference, blood pressure, lipids, HbA_{1c}, and fasting serum glucose at baseline were observed.

Diagnosis and Main Criteria for Inclusion: The study population included adult subjects ≤70 years of age with a BMI ≥27 and ≤45 kg/m^2 with ≥2 of the following obesity-related co-morbid conditions: elevated blood pressure or requirement for ≥2 antihypertensive medications, elevated TG or requirement for ≥2 lipid-lowering medications, elevated fasting blood glucose or diabetes, and/or waist circumference ≥102 cm for men or ≥88 cm for women. Subjects with diabetes did not have a lower limit on the BMI inclusion criterion.

4.2.3.2 Demographics at Baseline and Subject Disposition

In study OB-303, which included subjects with obesity-related co-morbidities, subjects with co-morbidities were balanced across treatment groups **(Table 4)**.

Table 4. Demographic and Baseline Characteristics (Randomized Set, Study OB-303)

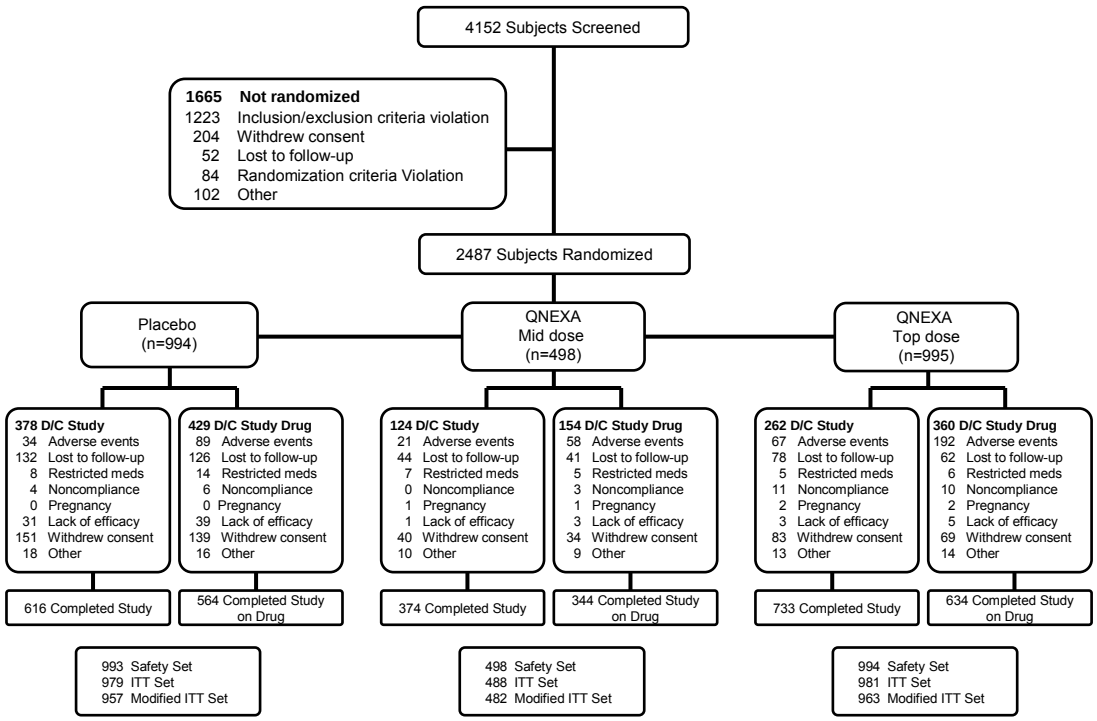
	Placebo (N=994)	QNEXA Mid (N=498)	QNEXA Top (N=995)	Total (N=2487)
Age, years				
N	994	498	995	2487
Mean (SD)	51.2 (10.25)	51.1 (10.43)	51.0 (10.65)	51.1 (10.44)
Sex, n (%)				
Female	695 (69.9)	349 (70.1)	693 (69.6)	1737 (69.8)
Male	299 (30.1)	149 (29.9)	302 (30.4)	750 (30.2)
Race, n (%)				
Caucasian	861 (86.6)	429 (86.1)	850 (85.4)	2140 (86.0)
African American	114 (11.5)	56 (11.2)	122 (12.3)	292 (11.7)
Asian	6 (0.6)	5 (1.0)	11 (1.1)	22 (0.9)
American Indian or Alaskan native	4 (0.4)	6 (1.2)	8 (0.8)	18 (0.7)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.4)	3 (0.3)	7 (0.3)
Other	12 (1.2)	5 (1.0)	8 (0.8)	25 (1.0)
Weight, kg				
N	993	498	994	2485
Mean (SD)	103.3 (18.09)	102.6 (18.18)	103.0 (17.58)	103.1 (17.90)
Height, cm				
N	993	498	994	2485
Mean (SD)	167.4 (9.82)	168.0 (9.77)	167.5 (9.46)	167.5 (9.66)
Body mass index, kg/m^2				
N	993	498	994	2485
Mean (SD)	36.7 (4.57)	36.2 (4.44)	36.6 (4.53)	36.6 (4.53)
Waist circumference, cm				
N	993	498	994	2485
Mean (SD)	113.4 (12.24)	112.6 (12.46)	113.2 (12.23)	113.2 (12.28)
Low-density lipoprotein cholesterol, mg/dL				
N	990	498	992	2480
Mean (SD)	123.8 (36.09)	120.8 (33.83)	123.7 (35.52)	123.1 (35.42)
High-density lipoprotein cholesterol, mg/dL				
N	993	498	994	2485
Mean (SD)	48.8 (13.76)	48.5 (12.80)	49.0 (13.72)	48.9 (13.55)
Total cholesterol, mg/dL				
N	993	498	994	2485
Mean (SD)	205.3 (41.67)	201.6 (37.91)	205.1 (40.39)	204.5 (40.44)
Triglycerides, mg/dL				
N	993	498	994	2485
Mean (SD)	163.6 (75.76)	161.2 (72.37)	162.0 (73.43)	162.5 (74.14)
Total cholesterol/HDL cholesterol ratio				
N	993	498	994	2485
Mean (SD)	4.49 (1.48)	4.38 (1.26)	4.44 (1.32)	4.45 (1.37)
Fasting serum glucose, mg/dL				
N	990	498	988	2476
Mean (SD)	106.5 (23.49)	105.8 (20.72)	105.9 (21.63)	106.1 (22.21)
Hemoglobin A_{1c}, %				
N	989	498	991	2478
Mean (SD)	5.9 (0.79)	5.8 (0.71)	5.9 (0.76)	5.9 (0.76)

	Placebo (N=994)	QNEXA Mid (N=498)	QNEXA Top (N=995)	Total (N=2487)
Systolic blood pressure, mm Hg				
N	993	498	994	2485
Mean (SD)	128.9 (13.53)	128.3 (13.84)	127.9 (13.37)	128.4 (13.53)
Diastolic blood pressure, mm Hg				
N	993	498	994	2485
Mean (SD)	81.1 (9.24)	80.6 (8.76)	80.1 (9.12)	80.6 (9.10)
Hypertension				
n (%)	524 (52.8)	261 (52.4)	520 (52.3)	1305 (52.5)
Dyslipidemia				
n (%)	354 (35.6)	180 (36.1)	363 (36.5)	897 (36.1)
Diabetes				
n (%)	159 (16.0)	68 (13.7)	166 (16.7)	393 (15.8)
History of depression				
n (%)	179 (18.0)	81 (16.3)	165 (16.6)	425 (17.1)
History of major depression				
n (%)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)

QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

A total of 2487 subjects were assigned randomly to treatment **(Figure 10)**. In total, 1723 (69.3%) subjects completed all study visits, and 764 (30.7%) subjects discontinued from the study. The percentages of subjects who completed the study were 62.0% in the placebo group, 75.1% in the QNEXA Mid dose group, and 73.7% in the Top dose group. Of the 2487 randomized subjects, 1542 (62.0%) subjects completed all study visits on study drug. The percentages of subjects who completed the study on study drug by treatment were 56.7% in the placebo group, 69.1% in the QNEXA Mid dose group, and 63.7% in the Top dose group. In total, 181 subjects completed study visits off study drug.

Figure 10. Subject Disposition in Study OB-303



Subjects may be counted in both discontinuation sections.
D/C=discontinued; ITT=intent-to-treat; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid dose, 7.5/46 mg; QNEXA Top dose, 15/92 mg.

4.3 Results and Integrated Efficacy Summary Across the QNEXA Phase 3 Program

In the analysis of the Phase 3 trial results, weight loss data are presented from both the ITT-LOCF set as well as the Completers set. The Completers set illustrates subjects who remained on drug for 56 weeks of the study.

4.3.1 Weight Loss

Results across all three QNEXA Phase 3 trials were consistent with regard to weight loss. Treatment with QNEXA, at all dose levels tested, resulted in statistically significant dose-dependent weight loss from baseline compared with placebo. The magnitude and time course of

weight loss was comparable across trials. The proportions of subjects achieving defined categories of weight loss was higher among the QNEXA groups compared with placebo. Results from the categorical analysis of weight loss were consistent with those from the analysis of percent weight loss across all of the studies. In 1-year trials, the observed weight loss exceeded FDA guidance for weight management products **(Appendix 2)**, and no rebound weight gain was observed during the trial period.

For each dose level, the magnitude of the QNEXA treatment effect on percent weight loss was numerically larger for the subjects completing 1 year of treatment on drug than for the ITT population. In addition, no differences in weight loss were observed when subjects were stratified according to baseline demographic characteristics such as race or sex. Subgroup analyses indicated that weight loss comparable to the total population was achieved in subpopulations with co-morbidities such as diabetes, hypertension, or hypertriglyceridemia. Weight loss was comparable across all trials in subjects with and without depression or cardiovascular risk factors.

The proof-of-concept findings from study OB-201 were confirmed in study OB-301, which included two dose levels of the combination to assess opportunities for dosing flexibility. In study OB-301, a 6-month factorial study, treatment with QNEXA resulted in a significantly greater LS mean percent weight loss from baseline at Week 28 compared with placebo **(Table 5).** Importantly, study OB-301 demonstrated that the combination of phentermine and topiramate resulted in weight loss from baseline that exceeded weight loss obtained with either agent, at corresponding doses, as monotherapy.

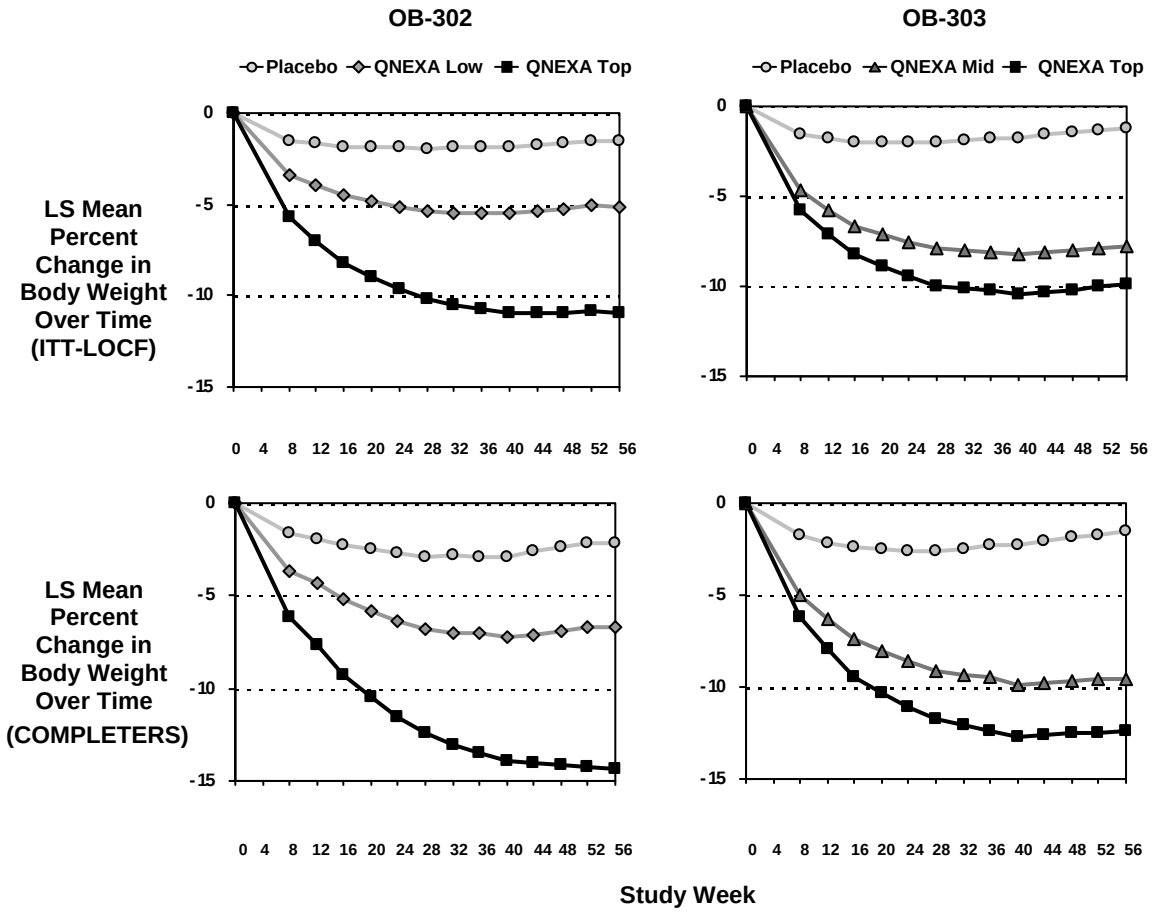
Table 5. Percent Weight Loss at Week 28: Treatment Comparisons — Study OB-301 (ITT-LOCF Set)

Treatment Comparison			N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)	
Tmt 1	vs	Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	p-value
QNEXA Top	vs	PHEN 15 mg	103	106	9.2 (0.61)	6.1 (0.61)	3.2 (0.83)	0.0001
	vs	TPM 92mg		105		6.4 (0.62)	2.8 (0.83)	0.0009
	vs	Placebo		103		1.7 (0.61)	7.5 (0.83)	<0.0001
QNEXA Mid	vs	PHEN 7.5 mg	103	104	8.5 (0.62)	5.5 (0.61)	3.0 (0.83)	0.0003
	vs	TPM 46 mg		102		5.1 (0.61)	3.3 (0.83)	<0.0001
	vs	Placebo		103		1.7 (0.61)	6.8 (0.83)	<0.0001
QNEXA Mid	vs	PHEN 15 mg	103	106	8.5 (0.62)	6.1 (0.61)	2.4 (0.82)	0.0037
	vs	TPM 92 mg		105		6.4 (0.62)	2.0 (0.83)	0.0150

Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and sex as fixed effects and baseline weight as a covariate.
ITT-LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate; SE=standard error; Tmt=treatment.
QNEXA Top, 15/92 mg; QNEXA Mid, 7.5/46 mg.

In studies OB-302 and OB-303, 1-year studies in obese subjects with and without co-morbidities, treatment with QNEXA Top dose resulted in weight loss that occurred rapidly and continued progressively through Week 56, at which time, subjects who had completed study OB-302 on drug lost 14.4% of baseline body weight, and subjects who had completed study OB-303 on drug lost 12.4% of baseline body weight (**Figure 11)**. For the QNEXA Low- and Mid-dose groups, mean percent weight loss progressively increased from baseline to Week 40 and then was relatively stable from Week 40 to the end of the study. Week 56 weight loss for subjects completing study on drug was 6.7% for QNEXA Low dose (OB-302) and 9.6% for QNEXA Mid dose (OB-303). For the placebo groups, mean percent weight loss was relatively stable from Week 28 to the end of the study, with the Week 56 mean percent weight loss averaging 2.1% in OB-302 and 1.6% in OB-303. **Figure 11** shows the mean percent weight loss over time by treatment group for the ITT-LOCF and Completers sets in studies OB-302 and OB-303.

Figure 11. Percent Weight Loss From Baseline Over Time (ITT-LOCF and Completers Sets)



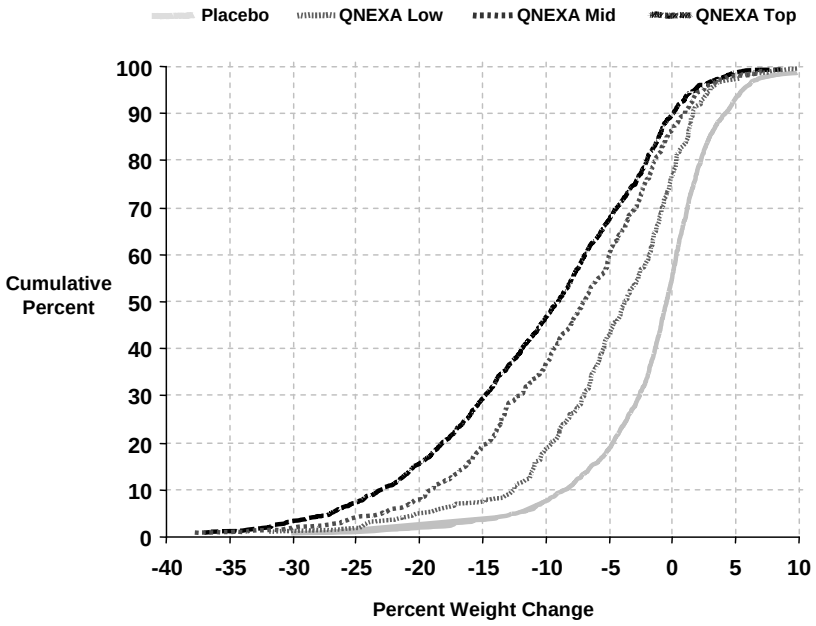
p<0.0001 vs placebo at all time points for all doses.
ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.1.1 Weight Loss by Benchmark Category

In addition to evaluating percent weight loss associated with treatment, differences between treatment groups in the percentage of subjects achieving certain weight loss benchmarks were evaluated. The cumulative distribution frequency plots for the 56-week Phase 3 studies, shown in **Figure 12** below, demonstrate that regardless of the benchmark selected, the percentage of subjects achieving this benchmark increased as the dose of QNEXA increased.

Figure 12. Cumulative Distribution of Percent Weight Change at Week 56 (ITT-LOCF and Completers Sets, 1-Year Cohort)

ITT-LOCF



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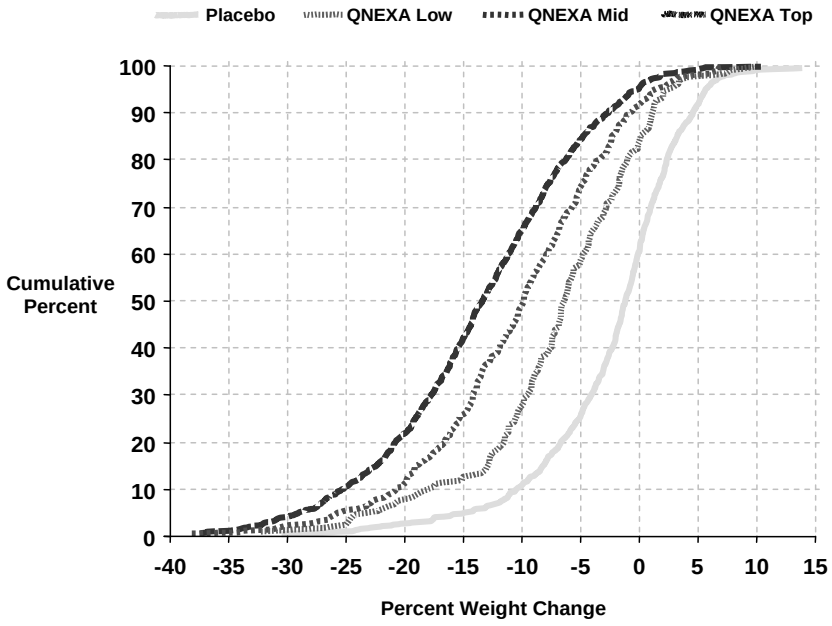


ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate. QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In study OB-301, a 6-month study, treatment with QNEXA Top dose (66.0%, 40.8%) and Mid dose (62.1%, 38.8%) both resulted in a higher proportion of subjects attaining weight loss of ≥5% and ≥10%, respectively, from baseline at Week 28 with LOCF compared with the individual components phentermine (15 mg, 46.2%, 20.8%; 7.5 mg, 43.3%, 12.5%) or topiramate (92 mg, 48.6%, 23.8%; 46 mg, 39.2%, 18.6%), or with placebo (15.5%, 6.8%).

Similar results with respect to proportions of subjects attaining weight loss benchmarks were obtained in year-long studies OB-302 and OB-303. The percent of subjects with ≥5%, ≥10%, and ≥15% weight loss was significantly greater in subjects treated with QNEXA compared with placebo at Week 56 **(Table 6)**. In addition, the proportion of subjects in each weight loss category increased according to QNEXA dose. Together, these studies demonstrated a dose relationship with drug therapy and support three dosing levels that provide a flexible dose regimen for QNEXA.

Table 6. Percentage of Subjects With ≥5%, ≥10%, and ≥15% Weight Loss at Study Endpoint — Individual Studies OB-302 and OB-303 (ITT-LOCF and Completers Sets)

Analysis Category	OB-302			OB-303		
	Placebo	QNEXA Low	QNEXA Top	Placebo	QNEXA Mid	QNEXA Top
ITT-LOCF [1]	n=498	n=234	n=498	n=979	n=488	n=981
≥5% weight loss	17.3	44.9*	66.7*‡	20.8	62.1*	70.0*‡
≥10% weight loss	7.4	18.8*	47.2*‡	7.4	37.3*	47.6*‡
≥15% weight loss	3.4	7.3†	32.3*‡	2.9	19.3*	28.8*‡
Completers non-LOCF [2]	n=239	n=137	n=297	n=557	n=338	n=625
≥5% weight loss	25.5	59.1*	83.5*‡	26.2	74.6*	85.1*‡
≥10% weight loss	13.0	27.7*	67.7*‡	9.7	49.1*	64.3*‡
≥15% weight loss	5.9	12.4†	48.1*‡	4.1	25.7*	39.2*‡

1. The ITT-LOCF analysis includes the last post-dose measurement for all subjects in the ITT set, regardless of whether or not the subject was on study drug.
2. The Completers non-LOCF analysis includes measurements from subjects who had an evaluation at the final study visit while on study drug or within 7 days of the last dose of study drug.
*p<0.001 vs placebo.
†p<0.05 vs placebo.
‡p<0.01 vs QNEXA Low (OB-302) or QNEXA Mid (OB-303).
ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate. QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

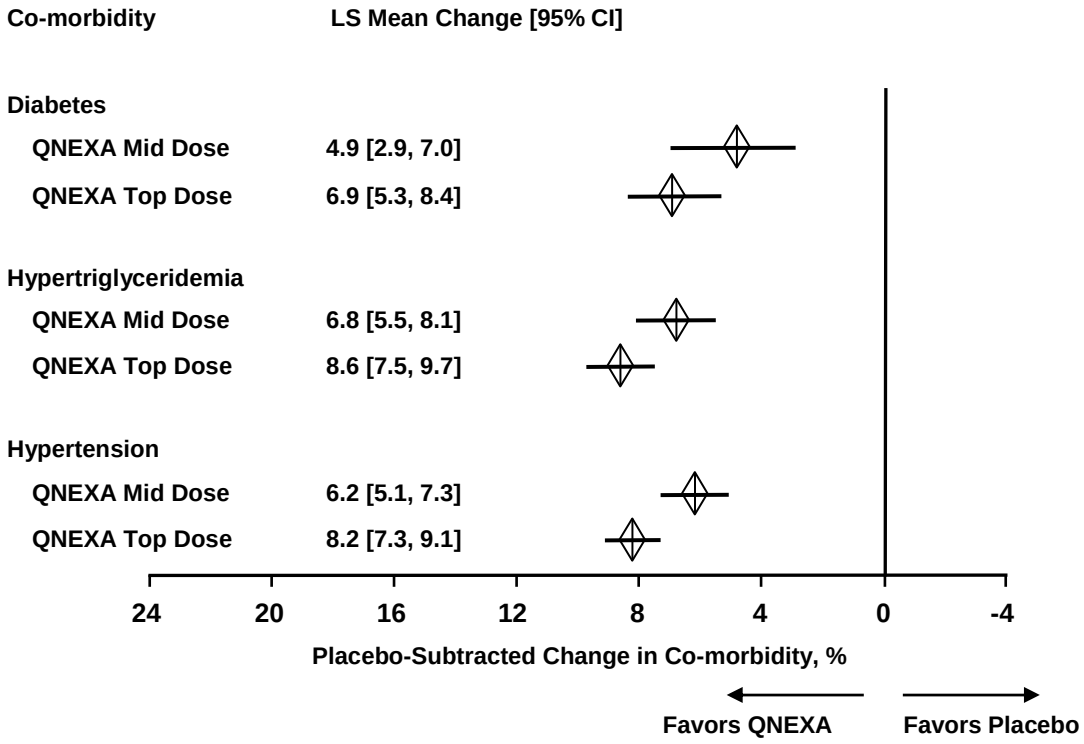
4.3.1.2 Weight Loss by Demographic Subgroups

Subgroup analysis of weight loss efficacy results in studies OB-302 and OB-303, in which subjects were stratified according to baseline BMI, age, race, or sex, indicated a dose-related weight loss associated with QNEXA therapy, but no differences in weight loss were observed between demographic subgroups.

4.3.1.3 Weight Loss by Weight-Related Co-Morbidity Status at Baseline

Subgroup analysis of subjects with co-morbidities in study OB-303 indicated that statistically significantly greater weight loss was observed in subjects treated with QNEXA compared with subjects treated with placebo. Weight loss in these subpopulations with diabetes, hypertriglyceridemia, or hypertension at baseline was comparable to the weight loss obtained with QNEXA in the total population **(Figure 13)**.

Figure 13. Placebo-Subtracted Weight Loss From Baseline at Study Endpoint, by Baseline Co-Morbidity Status, in Subjects Treated with QNEXA — Study OB-303 (ITT-LOCF Set)



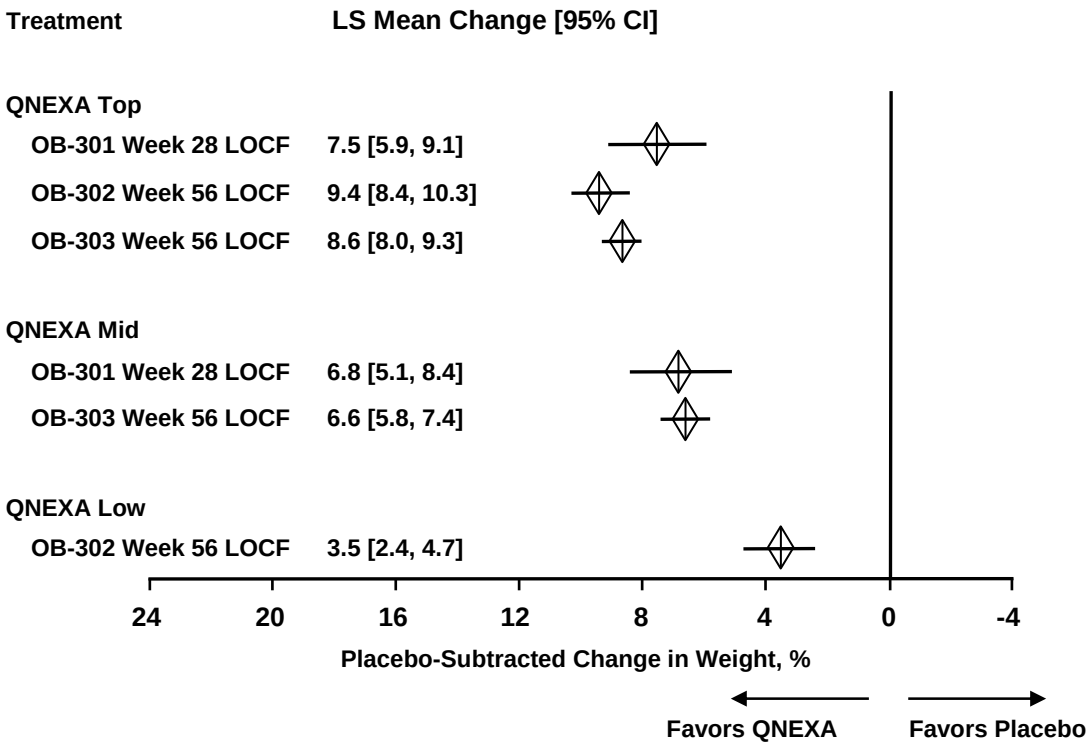
CI=confidence interval; ITT-LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.1.4 Summary of Weight Loss Efficacy

The consistency across trials with respect to statistically significant weight loss, relative to placebo, as well as the dose responsiveness of the effect of QNEXA on weight loss is indicated in forest plots of results from the Phase 3 studies. **Figure 14** shows the results for percent weight loss, relative to placebo, at study endpoint for the ITT-LOCF set and for the Completers set across the Phase 3 studies.

Figure 14. Placebo-Subtracted Weight Loss From Baseline at Study Endpoint in Subjects Treated with QNEXA — Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF and Completers Sets)

ITT-LOCF



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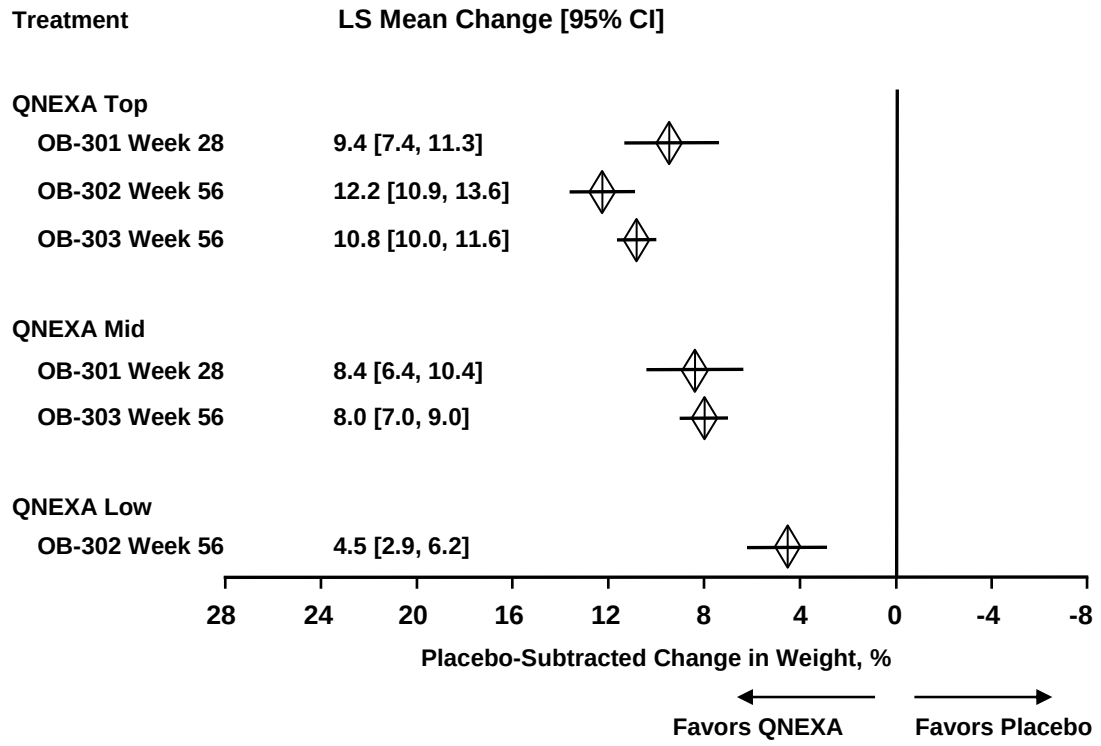


CI=confidence interval; ITT LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.2 Responders

Responders were defined as subjects who achieved ≥5% weight loss at baseline. Based on an ITT population, approximately 30% to 40% of QNEXA-treated subjects (at any dose level) were nonresponders, because they did not achieve the categorical weight loss of 5%. These nonresponders were demographically similar to the responders; however, they had a higher incidence of treatment-emergent adverse events (TEAEs), and had higher overall rates of dropout and discontinuation due to TEAEs than subjects in the responder group (Appendix 8). Analysis of weight loss by quintile at 12 weeks suggests that a predictive measure for low responders is approximately 3% weight loss at 12 weeks.

4.3.3 Waist Circumference and Body Composition

Waist Circumference

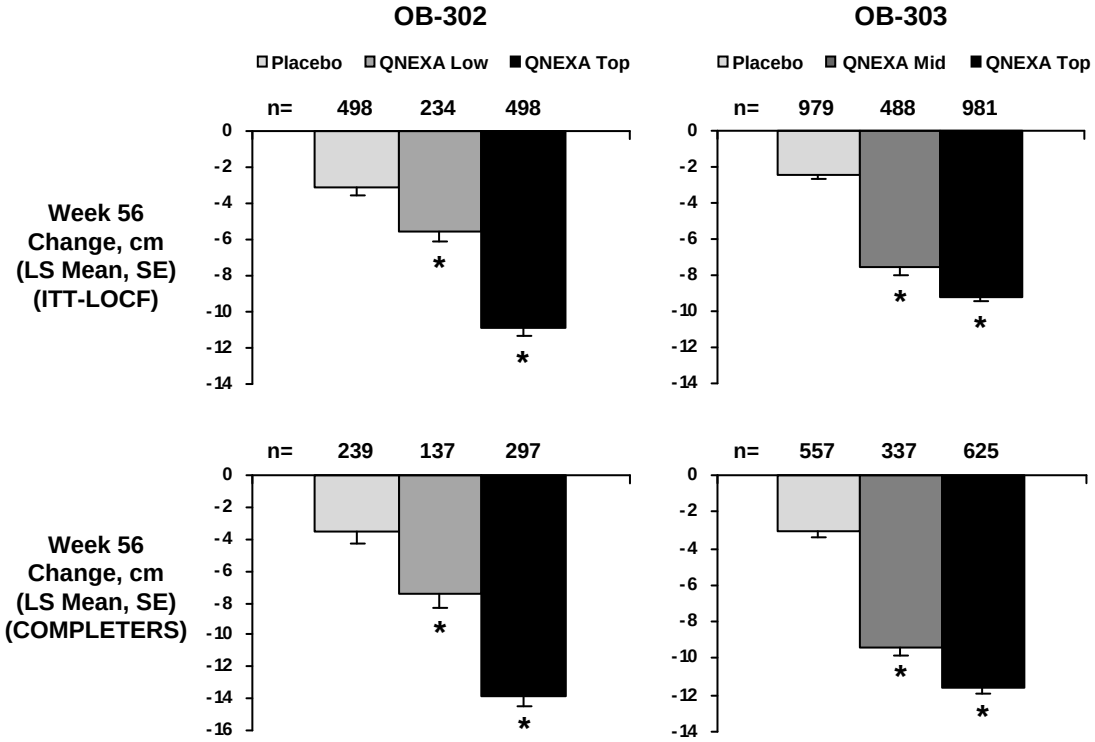
In study OB-301, the reduction from baseline in LS mean waist circumference at Week 28 was -8.7 cm for the QNEXA Top-dose group, -8.8 cm for the QNEXA Mid-dose group, and -3.3 cm for the placebo group. The magnitude of waist reduction was lower in cohorts treated with corresponding monotherapy at the same dose.

In study OB-302, the reduction from baseline at Week 56 in LS mean waist circumference was significantly greater in the QNEXA Top-dose group (-10.9 cm)[-13.9 cm][1] compared with the Low-dose group (-5.6 cm)[-7.5 cm] and the placebo group (-3.1 cm)[-3.6 cm] ($p<0.0001$ and $p=0.0006$, vs placebo, respectively, in the ITT-LOCF set; $p<0.0001$ and $p=0.0002$, vs placebo, respectively, in the Completers set) **(Figure 15)**.

In study OB-303, the reduction from baseline in waist circumference was significantly greater in the QNEXA Top-dose group (-9.2 cm)[-11.6 cm] compared with the QNEXA Mid-dose group (-7.6 cm)[-9.4 cm] and placebo group (-2.4 cm)[-3.1 cm] at Week 56 ($p<0.0001$ vs placebo, in each case) **(Figure 15)**.

[1] Parentheses indicate ITT-LOCF set data; brackets indicate Completers set data.

Figure 15. Waist Circumference Change From Baseline at Study Endpoint — Individual Studies OB-302 and OB-303 (ITT-LOCF and Completers Sets)



*p<0.0001 (Mid and Top doses), p=0.0006 (Low dose, ITT-LOCF), p=0.0002 (Low dose, Completers) vs placebo for each.
n=Number of subjects reaching threshold at Week 56.
Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and sex as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate; SE=standard error.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Body Composition

A subset of subjects from participating sites in studies OB-302 and OB-303 underwent dual energy x-ray absorptiometry scanning for evaluation of changes in body composition. Mean decreases in percent adiposity and mean increases in percent lean body mass from baseline were larger for the QNEXA Top-dose group compared with placebo in the OB-302 subset and larger for both QNEXA groups compared with placebo in the OB-303 subset. QNEXA-associated weight loss was primarily due to a reduction in fat mass and not lean body mass.

4.3.4 Weight-Related Co-Morbidities

The effect of QNEXA treatment on important weight-related co-morbidities was assessed throughout the clinical program. The effects of QNEXA were evaluated in the whole study population regardless of baseline status (patients with and without co-morbidities), and then specifically, in pre-existing disease populations, such as subjects with hypertension, hypertriglyceridemia, and type 2 diabetes. The analysis of disease populations at baseline based on prespecified protocol inclusion criteria provided a more relevant examination of QNEXA's effects on each disease population. This approach was followed in the design of the Phase 2 studies (diabetes and sleep apnea) as well as the Phase 3 program (OB-303; hypertension, hypertriglyceridemia, and diabetes).

General improvements in weight-related co-morbidities, such as cardiovascular and lipid co-morbidities, were consistently demonstrated across studies and across the entire population. At both 6 months and 1 year, treatment with any of the three doses of QNEXA resulted in statistically significant decreases from baseline in systolic blood pressure compared with placebo in the ITT population. Significant improvements were also demonstrated in lipid profiles, glycemic indices, and inflammatory markers.

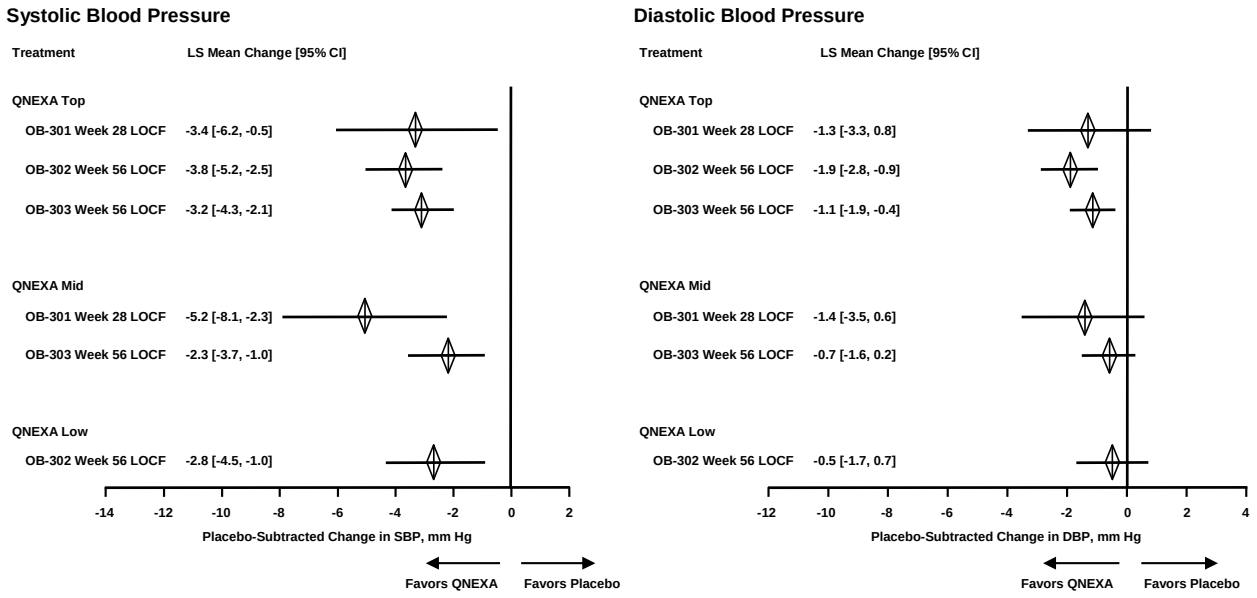
In subjects with co-morbidities at baseline, as in study OB-303, greater and dose-related improvements in cardiovascular, metabolic, and inflammatory disease markers were achieved. In the case of subgroups of subjects with hypertension or diabetes, QNEXA-related improvements in blood pressure or glycemic parameters, respectively, occurred concomitantly with reductions in medications taken by subjects to treat these co-morbidities. In general, a greater burden of weight-related co-morbidity at baseline was associated with a greater degree of disease improvement with QNEXA therapy, as well as a significant reduction in medications required to treat the associated co-morbidity.

4.3.4.1 Blood Pressure

Reductions from baseline in systolic blood pressure were consistently observed in subjects treated with QNEXA compared with subjects treated with placebo at study endpoint across all three Phase 3 studies (all statistically significant vs placebo) **(Figure 16)**.

Reductions from baseline in diastolic blood pressure were consistently observed in subjects treated with QNEXA compared with subjects treated with placebo at study endpoint across all three Phase 3 studies (QNEXA Top dose in studies OB-302 and OB-303 statistically significant vs placebo**) (Figure 16)**.

Figure 16. Placebo-Subtracted Systolic and Diastolic Blood Pressure Change From Baseline at Study Endpoint in Subjects Treated with QNEXA — Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



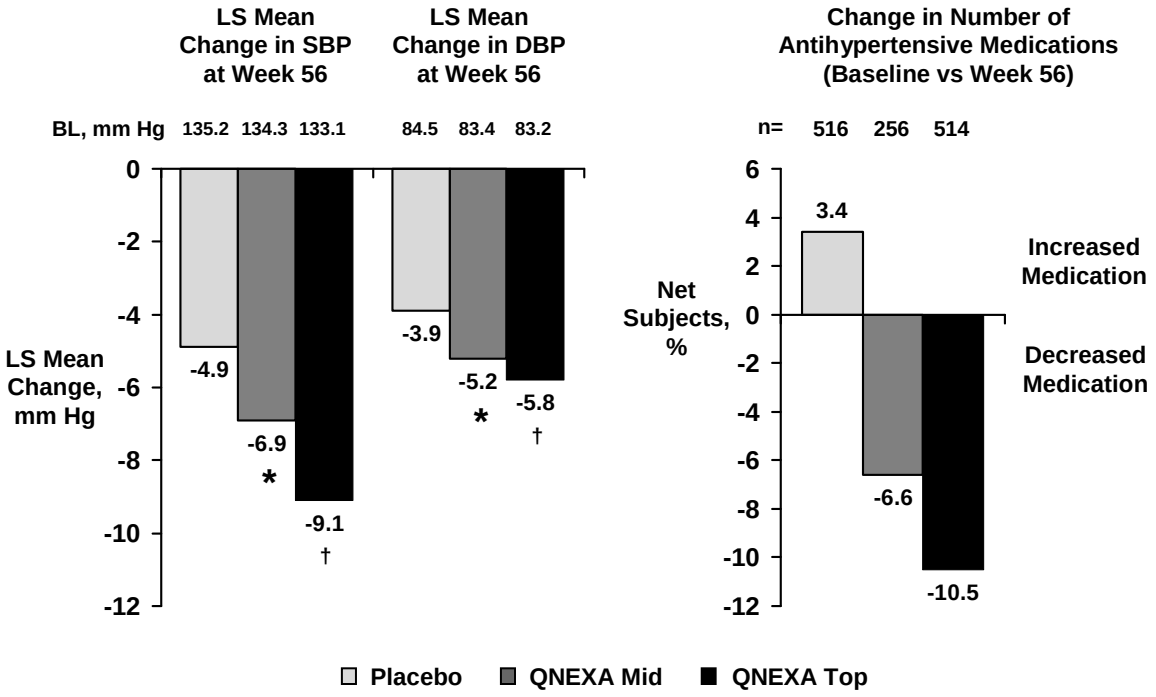
CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In study OB-303, 1286 (52.5%) subjects in the ITT set met the protocol-specified criteria for hypertension (SBP 140-160 mm Hg [130-160 mm Hg, if diabetic]; DBP 90-100 mm Hg [85-100 mm Hg, if diabetic]; or use of two or more anti-hypertensive medications to control blood pressure). For this subpopulation of subjects with hypertension, the LS mean percent weight loss at Week 56 with LOCF was 10.1% with QNEXA Top-dose treatment, 8.2% with QNEXA Mid dose, and 1.9% with placebo. These results were similar to those observed for the overall OB-303 ITT set (1.2% with placebo, 7.8% with QNEXA Mid dose, and 9.8% with QNEXA Top dose).

Figure 17 presents the results for changes in SBP and DBP at Week 56 with LOCF for the subgroups of subjects with hypertension at baseline in study OB-303.

The percentage of subjects with hypertension who had an increase in the number of concomitant antihypertensive medications from baseline to the end of study was higher in the placebo group than in the QNEXA groups. Conversely, the percentage of subjects with a decrease in the number of concomitant antihypertensive medications was higher in the QNEXA groups than in the placebo group.

Figure 17. Blood Pressure Change From Baseline at Week 56 in Subjects With Hypertension — Study OB-303 (ITT-LOCF Set)

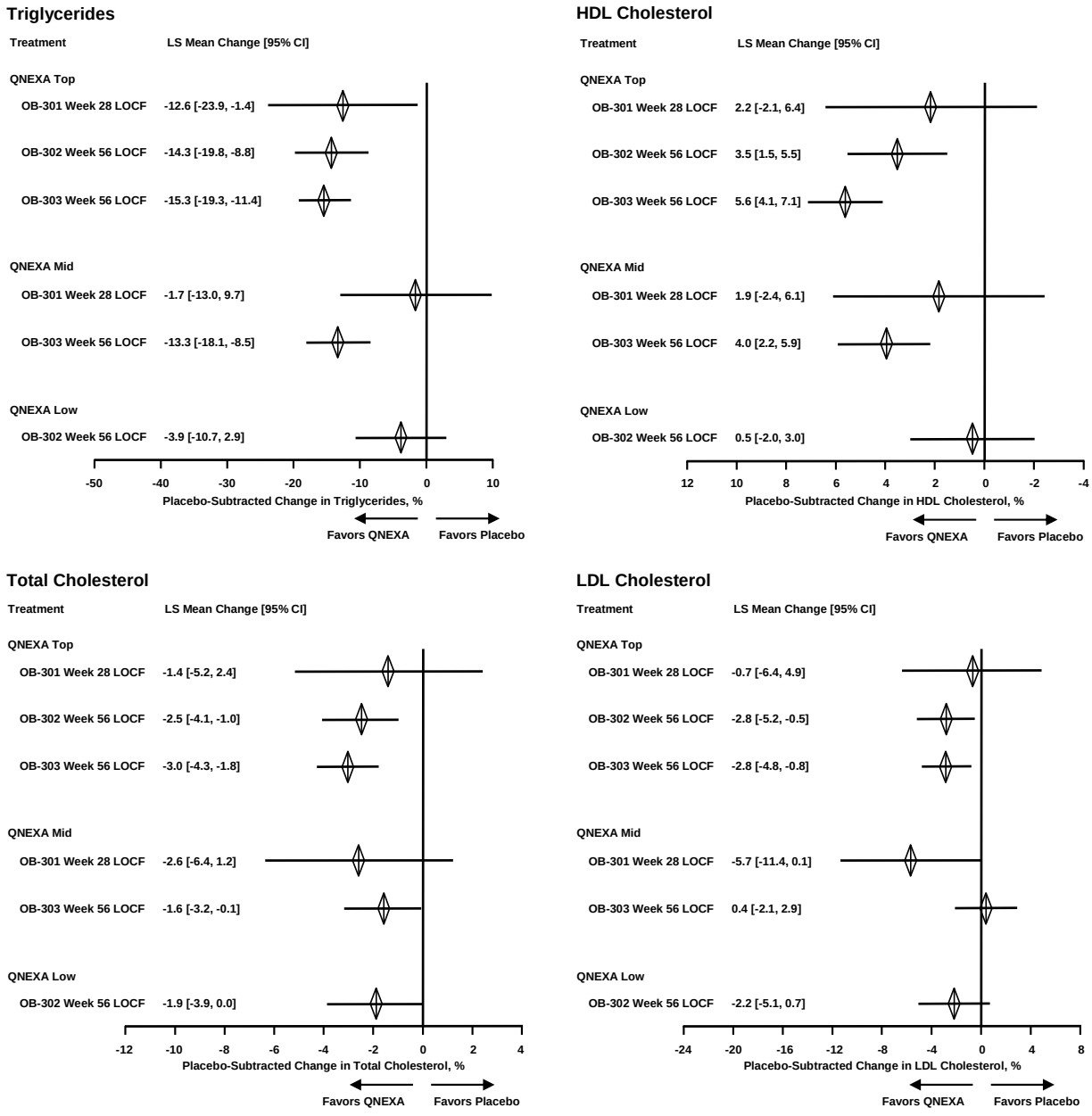


*p<0.05 vs placebo.
†p<0.001 vs placebo.
BL=baseline; BP=blood pressure; ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.4.2 Lipid Parameters

Mean TG, HDL-C, TC, and LDL-C levels were improved from baseline in subjects treated with QNEXA, compared with subjects treated with placebo, at study endpoint across all Phase 3 trials in the ITT-LOCF population **(Figure 18).** In subjects treated with QNEXA Top dose, TG levels were statistically significantly different from subjects treated with placebo across all three Phase 3 trials. In subjects treated with QNEXA Top dose, TC, HDL-C, and LDL-C levels were statistically significantly different from subjects treated with placebo in studies OB-302 and OB-303.

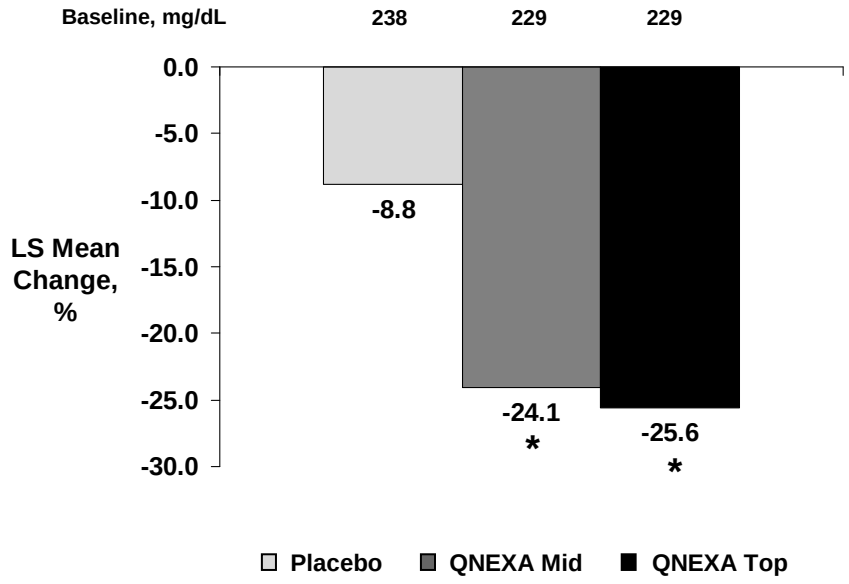
Figure 18. Placebo-Subtracted Lipid Parameters Changes From Baseline at Study Endpoint in Subjects Treated With QNEXA — Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In study OB-303, 885 (36.2%) subjects in the ITT set met the protocol-specified criteria for hypertriglyceridemia (TG ≥200 and ≤400 mg/dL, or use of more than 1 lipid-lowering medication). For subjects with hypertriglyceridemia in study OB-303, treatment with either QNEXA Mid dose or Top dose resulted in significant decreases in TG levels (**Figure 19)** and significant increases in HDL-C levels relative to placebo (**Table 7).** Treatment with QNEXA Top dose also resulted in a statistically significant decrease in TC relative to placebo (**Table 7)**.

Figure 19. Fasting Triglycerides Change From Baseline at Week 56 in Subjects With Hypertriglyceridemia — Study OB-303 (ITT-LOCF Set)



*p<0.0001 vs placebo.
ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate. QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Table 7. Lipid Parameters Change From Baseline at Week 56 in Subjects With Hypertriglyceridemia — Study OB-303 (ITT-LOCF Set)

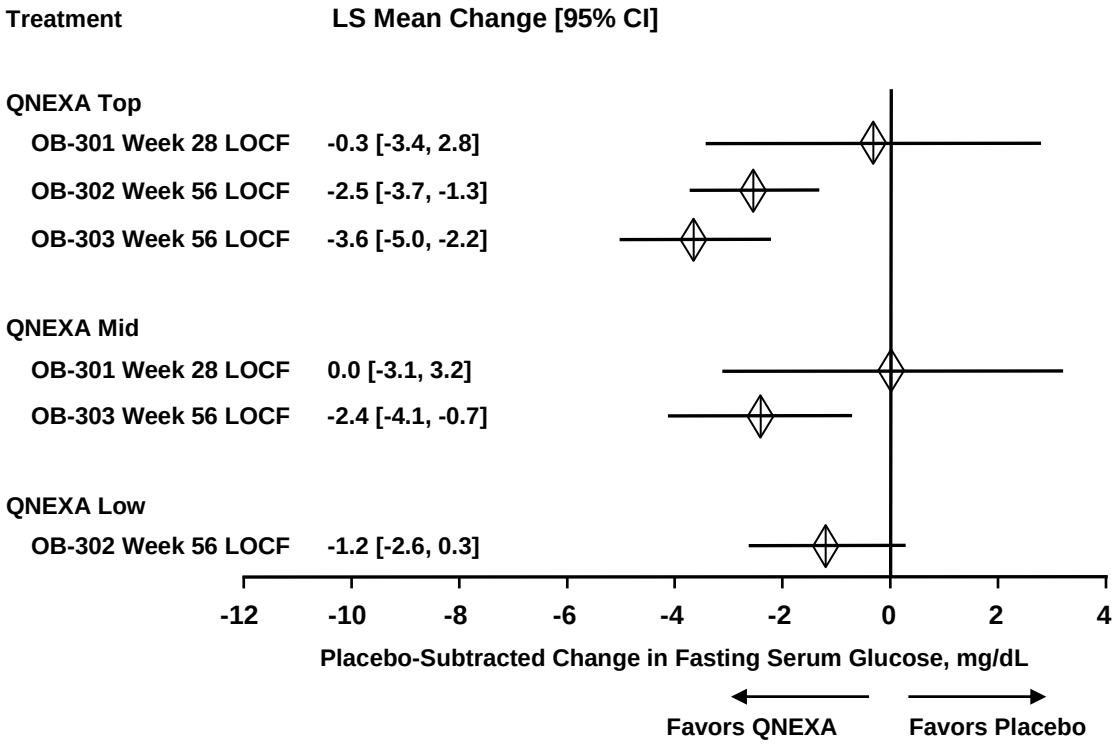
	Placebo (N=349)		QNEXA Mid (N=179)		QNEXA Top (N=357)	
	Baseline [1]	Week 56 Percent Change [2]	Baseline [1]	Week 56 Percent Change [2]	Baseline [1]	Week 56 Percent Change [2]
Triglycerides, mg/dL	238.4	-8.8	229.2	-24.1*	229.2	-25.6*
LDL cholesterol, mg/dL	124.0	-3.6	114.6	0.7	122.2	-4.3
Total cholesterol, mg/dL	214.3	-4.9	203.4	-5.7	211.9	-7.8†
HDL cholesterol, mg/dL	42.5	2.8	42.9	9.5*	43.9	10.7*

1. Mean baseline values.
2. Least-squares mean percent changes from baseline to Week 56 with LOCF.
*p<0.001 vs placebo.
†p<0.05 vs placebo.
HDL=high-density lipoprotein; ITT-LOCF=intent-to-treat–last observation carried forward; LDL=low-density lipoprotein; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.4.3 Glycemic Parameters

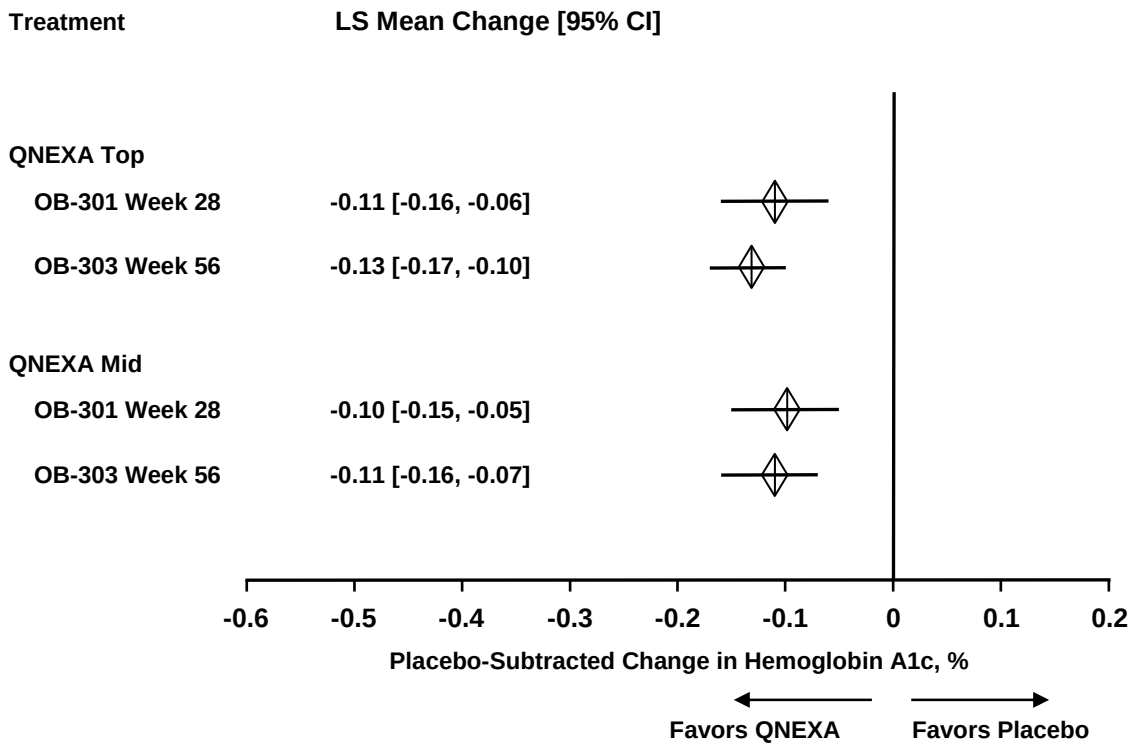
Treatment with QNEXA in Phase 3 studies improved the glycemic profiles of all subjects (ITT population) regardless of whether baseline status was normal, prediabetic, or diabetic. Improvements in glycemic parameters (fasting glucose and HbA_{1c}) occurred across all trials **(Figures 20 and 21).** In non-diabetic subjects, small but significant improvements were observed in HbA_{1c} and fasting glucose in subjects treated with QNEXA compared with placebo in OB-301, OB-302, and OB-303. Statistically significant improvements in HBA_{1c} from baseline at study endpoint relative to placebo, occurred across trials OB-301 and OB-303 in subjects treated with QNEXA. Statistically significant improvements in fasting serum glucose from baseline at study endpoint, relative to placebo, occurred across trials OB-302 and OB-303 in subjects treated with QNEXA Top-dose.

Figure 20. Placebo-Subtracted Fasting Serum Glucose Change From Baseline at Study Endpoint in Subjects Treated With QNEXA — Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI=confidence interval; ITT-LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

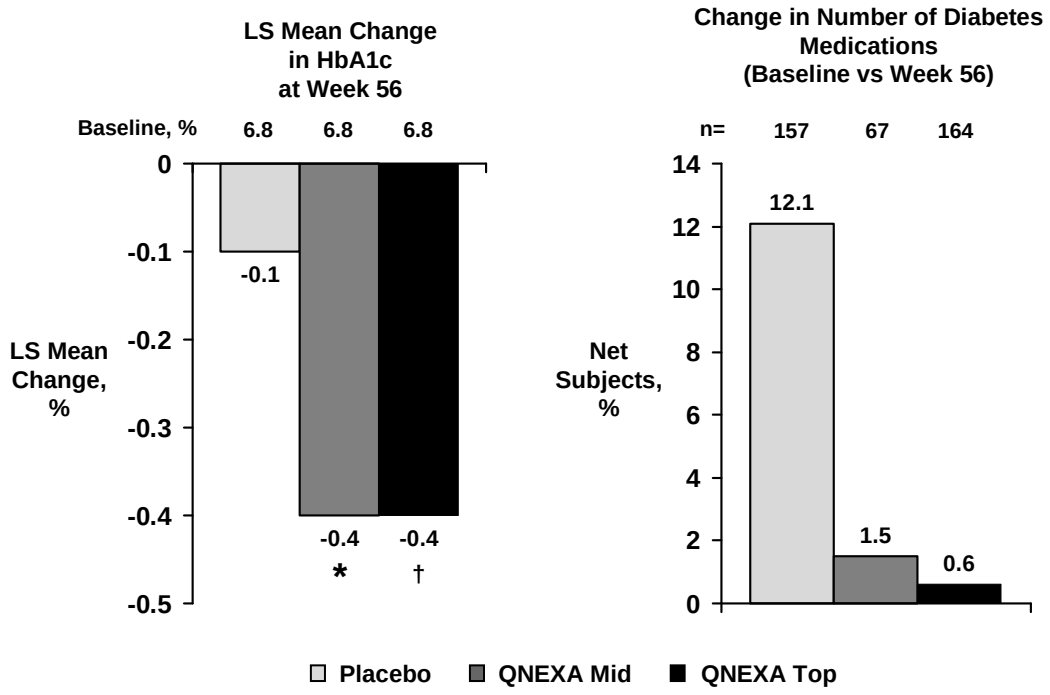
Figure 21. Placebo-Subtracted Hemoglobin A_{1c} Change From Baseline at Study Endpoint in Subjects Treated With QNEXA – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



Note: Study 302 included only nondiabetic subjects.
CI=confidence interval; ITT-LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In study OB-303, 388 (15.8%) subjects in the ITT set met the protocol-specified criteria for diabetes (fasting blood glucose >126 mg/dL, glucose >200 mg/dL at 2 hours post-glucose challenge during oral glucose tolerance testing), based on their Medical History electronic Case Report Form. For subjects with diabetes at baseline in study OB-303, treatment with QNEXA resulted in statistically significant decreases in HbA_{1c} relative to placebo **(Figure 22)**. Treatment with QNEXA also resulted in larger decreases in fasting serum glucose than placebo **(Table 8)**; however, the treatment comparisons were not statistically significant.

Figure 22. Hemoglobin A_{1c} and Antidiabetic Medications Change From Baseline at Week 56 in Subjects With Diabetes — Study OB-303 (ITT-LOCF Set)



*p=0.0288 vs placebo.
†p=0.0043 vs placebo.
COM=combination of phentermine and topiramate; ITT-LOCF=intent-to-treat–last observation carried forward;.

Table 8. Hemoglobin A_{1c} and Fasting Glucose Changes From Baseline at Study Endpoint in Subjects With Diabetes — Individual Studies OB-303 and OB-202 (ITT-LOCF Set)

	OB-303			OB-202	
	Placebo (N=157)	QNEXA Mid (N=67)	QNEXA Top (N=164)	Placebo (N=55)	QNEXA Top (N=75)
Baseline HbA_{1c}, %	6.8	6.8	6.8	8.6	8.7
Change in HbA_{1c}, %	-0.1	-0.4*	-0.4*	-0.6	-1.1†
Baseline fasting glucose, mg/dL	136.7	134.2	131.1	174.0	174.7
Change in fasting glucose, mg/dL	-5.6	-9.7	-11.9	-7.6	-32.6‡
Subjects with:					
Antidiabetic medications added, %	14.6	4.5	4.3	25	14
Antidiabetic medications discontinued, %	2.5	3.0	3.7	12	24

*p<0.05 vs placebo.
†p=0.0007 vs placebo.
‡p=0.0001 vs placebo.
HbA_{1c}=hemoglobin A_{1c}; ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

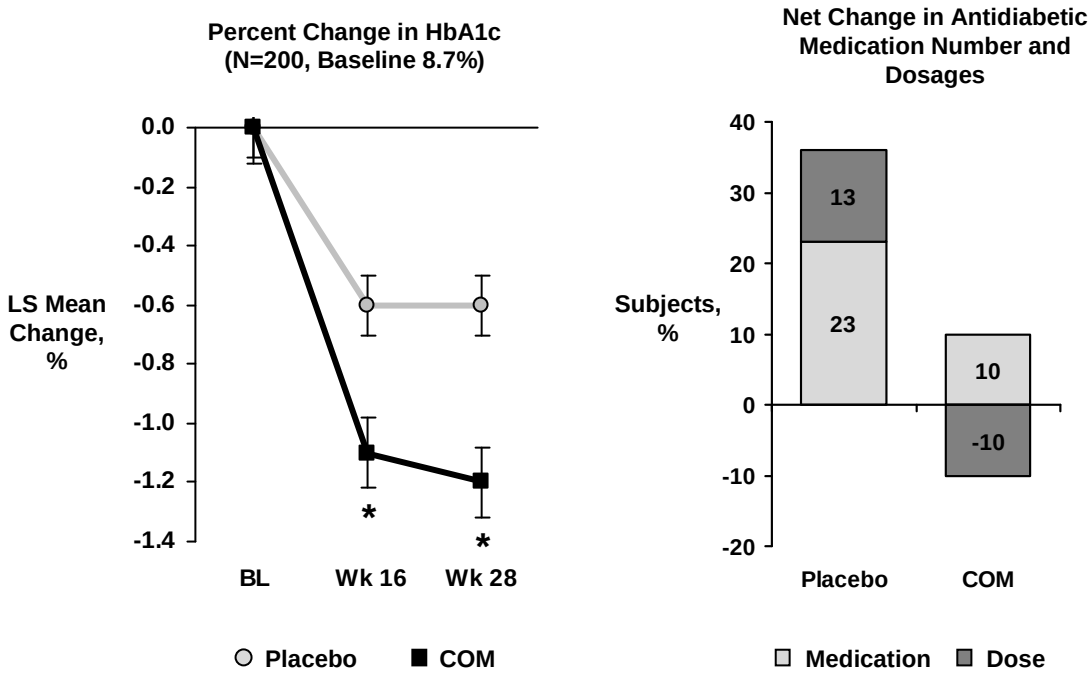
Also presented in **Table 8** are the results from study OB-202. Study OB-202, a Phase 2, randomized, double-blind, placebo-controlled, multicenter trial compared phentermine/topiramate combination therapy with placebo in patients with type 2 diabetes mellitus after 28 weeks of treatment. The primary endpoint was change in HbA_{1c}. A total of 210 eligible subjects were randomized to receive daily treatment with placebo or the combination of phentermine 15 mg and topiramate 100 mg. Phentermine was administered in the morning with breakfast, and topiramate was administered in the afternoon.

The study population included adult subjects ≤70 years of age who had a BMI ≥27 kg/m^2 and ≤45 kg/m^2 and type 2 diabetes that was controlled by diet or oral antidiabetic medications. Enrolled subjects represented a wide spectrum of the diabetic population in terms of duration and severity of disease and in terms of medications to control disease permitted at baseline. Notably, this study included a population of subjects with more advanced diabetes than study OB-303: Overall, 32% of subjects had been diagnosed with diabetes for 5 to 10 years and 27% for more than 10 years. Subjects enrolled in the study were required per protocol to have a baseline HbA_{1c} of 7% to 12%, inclusive and the mean for the study was 8.7%. Forty-seven percent of subjects

were taking two or more diabetic medications and 20% of subjects were naïve to diabetic medication. Additionally, the study group was racially diverse, and most subjects reported Hispanic or Latino ethnicity. The study group contained a high proportion of individuals of color, reflective of the overall population with type 2 diabetes.

The LS mean change in HbA_{1c} from baseline (mean 8.7%) to Week 28 with LOCF for the ITT population was -1.1% for the phentermine/topiramate 15/100 mg group and -0.6% for the placebo group **(Figure 23)**. The difference from baseline at Week 28 between active treatment and placebo was statistically significant (p=0.0007). This HbA_{1c} reduction was greater than the reduction obtained in subjects in the OB-303 trial.

Figure 23. Hemoglobin A_{1c} and Antidiabetic Medications Changes From Baseline at Week 28 in Subjects With Diabetes — Study OB-202 (ITT-LOCF Set)



*p<0.0001 vs placebo.
BL=baseline; COM=combination of phentermine and topiramate; HbA_{1c}=hemoglobin A_{1c}; ITT-LOCF=intent-to-treat–last observation carried forward;

The LS mean change in fasting blood glucose from baseline to Week 28 with LOCF for the ITT population was -7.6 mg/dL for the placebo group and -32.6 mg/dL for the phentermine/topiramate 15/100 mg group. The difference from baseline at Week 28 between treatment groups and placebo was statistically significant ($p<0.0001$).

The LS mean change in fasting insulin from baseline to Week 28 with LOCF for the ITT population was 7.0 µIU/mL for the placebo group and 3.5 µIU/mL for the phentermine/topiramate 15/100 mg group; the difference from baseline at Week 56 between treatment groups was not statistically significant ($p=0.1147$).

Furthermore, treatment comparisons between phentermine/topiramate 15/100 mg and placebo were statistically significant for changes in insulin sensitivity indices at Week 28. Significantly greater ($p<0.0001$) absolute weight loss, categorical weight loss, and reduction in waist circumference were also observed in subjects in the phentermine/topiramate treatment group, and consistent with the Phase 3 studies, significant improvements in blood pressure, triglycerides and other cardiometabolic risk factors were obtained.

In both study OB-303 and study OB-202, the percentage of subjects with diabetes who had an increase in the number of concomitant antidiabetic medications from baseline to the end of study was higher in the placebo group than in the active treatment groups **(see Table 8, Figure 22, and Figure 23 above)**. In study OB-202, the percentage of subjects with a decrease in the number of concomitant antidiabetic medications was higher in the phentermine/topiramate treatment group than in the placebo group. In study OB-303, the percentages of subjects in each treatment group with a decrease in the number of concomitant antidiabetic medications were similar. Subjects in study OB-303 with diabetes at baseline had negligible increases in diabetes medications at Week 56.

Table 9 presents the results for changes in fasting insulin and insulin sensitivity parameters from baseline to Week 56 with LOCF for subjects in study OB-303. A large proportion of the OB-303 study population could appropriately be characterized as having impaired fasting glucose or impaired glucose tolerance at baseline. In this study, QNEXA treatment resulted in improvements in fasting insulin levels, decreases in insulin resistance as measured by

homeostatic model assessment of insulin resistance (HOMA-IR), and increases in insulin sensitivity during oral glucose tolerance testing.

Table 9. Fasting Insulin and Insulin Sensitivity Parameters Changes From Baseline at Week 56 — Study OB-303 (ITT-LOCF Set)

	Placebo (N=925)		QNEXA Mid (N=464)		QNEXA Top (N=937)	
Parameter	Baseline [1]	Week 56 Change [2]	Baseline [1]	Week 56 Change [2]	Baseline [1]	Week 56 Change [2]
Fasting insulin, µIU/mL	17.8	0.7	18.0	-3.5*	18.4	-4.0*
HOMA-IR	5.15	0.46	4.94	-0.93*	5.30	-1.07*
Composite whole-body insulin sensitivity index	3.54	0.5	3.36	1.7*	3.65	2.0*

1. Mean baseline values.
2. Least-squares mean changes from baseline to Week 56 with LOCF.
*p<0.001 vs placebo.
HOMA-IR=homeostasis model assessment–insulin resistance; ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

The importance of these changes can be seen in data showing progression to type 2 diabetes during the Phase 3 studies. Among all subjects treated in Phase 3 trials who did not have a diagnosis of type 2 diabetes at study entry, emergence of type 2 diabetes (post-baseline fasting glucose level of ≥126 mg/dL or 2-hour glucose level of ≥200 mg/dL during oral glucose tolerance test [OGTT]) was observed in 9.9% of placebo-treated subjects compared with 6.6% of QNEXA-treated subjects (relative risk 0.66; 95% CI, 0.53-0.83). The annual incidence rate for type 2 diabetes was 13.8% in placebo subjects vs 8.1% in QNEXA-treated subjects. QNEXA treatment, therefore, resulted in a 41% decrease in the annual incidence of type 2 diabetes. In study OB-303, where the majority of subjects had impaired glucose tolerance at baseline, the results were even more dramatic. Progression to type 2 diabetes using the criteria described above was observed in 14.6% of subjects treated with placebo, 10.7% of subjects treated with QNEXA Mid dose, and 9.2% of subjects treated with QNEXA Top dose. The relative risk of diabetes progression between QNEXA Top dose and placebo was 0.63 (95% CI, 0.48-0.82) and the reduction in the annualized incidence rate was 46% (from 19.9% to 10.8%). Based on these reductions, the number needed to treat (NNT) to prevent one case of type 2 diabetes over a 1-year period is approximately 11 subjects.

4.3.5 Biomarkers of Cardiovascular Disease Risk

In study OB-303, the LS mean changes in C-reactive protein (CRP), adiponectin, and fibrinogen were statistically significant for all treatment groups. The treatment comparisons of QNEXA with placebo were statistically significant for changes in CRP. Treatment comparisons were not made for changes in adiponectin and fibrinogen.

High-sensitivity (hs)-CRP values were determined in subjects included in the 1-year cohort **(Table 10)**. A total of 3157 subjects had both baseline and Week 56/early termination (ET) hs-CRP values available (1179 on placebo and 1978 on any dose of QNEXA). Mean baseline hs-CRP was 7.28 mg/L (SD ± 9.96) in the 1-year cohort (median 4.8 mg/L), indicating an elevated level of cardiovascular risk.

Of the 3157 subjects with both baseline and Week 56/ET values for hs-CRP, 228 (7.2%) had levels <1 mg/L, 834 (26.4%) between 1 and 3 mg/L, and 2095 (66.3%) >3 mg/L.

By Week 56/ET, hs-CRP was reduced significantly in placebo, QNEXA Mid, and Top dose groups, but the magnitude of reduction was greater in the QNEXA Mid- and Top-dose groups (-2.8 and -2.8 mg/L, respectively) than in the placebo group (-0.7 mg/L). The change in hs-CRP in the Mid- and Top-dose groups represented a mean reduction of approximately 39% from their baseline values.

Changes in hs-CRP were also analyzed by stratification of baseline values into three groups (<1, 1-3, and >3 mg/L) corresponding to “low,” “intermediate,” and “elevated” cardiovascular risk. In those subjects with baseline hs-CRP >3 mg/L, the mean baseline hs-CRP was 10.15 mg/L (SD ± 11.17). Reductions in hs-CRP in these subjects were larger in magnitude: 4.6 and 4.4 mg/L, on QNEXA Mid and Top dose, respectively, representing a reduction of approximately 44% from baseline values. Reductions in the “low” and “intermediate” risk strata (those with baseline hs-CRP ≤3 mg/L) were not significant.

Table 10. High-Sensitivity C-Reactive Protein Change From Baseline at Week 56/ET in All Subjects and Subjects With Baseline Value >3 mg/L (Safety Set, 1-Year Cohort)

All subjects				
Time Point	**Placebo (N=1179)**	**QNEXA Low (N=181)**	**QNEXA Mid (N=440)**	**QNEXA Top (N=1357)**
Baseline hs-CRP, mg/L [1]	7.2	8.9	7.0	7.2
Week 56/ET, mg/L [1]	6.5	8.4	4.2	4.5
Week 56/ET change, mg/L [2]	-0.7	-0.5	-2.8	-2.8
Subjects with baseline value >3 mg/L				
Time Point	**Placebo (N=777)**	**QNEXA Low (N=147)**	**QNEXA Mid (N=275)**	**QNEXA Top (N=896)**
Baseline hs-CRP, mg/L [1]	10.1	10.6	10.2	10.1
Week 56/ET, mg/L [1]	8.5	9.7	5.7	5.8
Week 56/ET change, mg/L [2]	-1.6	-0.9	-4.6	-4.4

Includes data from OB-202, DM-230, OB-302, and OB-303.
1. Mean values.
2. Mean changes from baseline to Week 56/ET.
ET=early termination; hs-CRP=high-sensitivity C-reactive protein; ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.6 Liver Enzymes

In study OB-302, LS mean decreases from baseline in alanine transaminase (ALT) were larger for the QNEXA groups than for the placebo groups **(Table 11).** Mean decreases in aspartate transaminase (AST) were only observed in the QNEXA Top-dose group. In study OB-303, mean decreases from baseline in ALT were larger for the QNEXA groups than for the placebo group. Decreases from baseline in AST were also observed for the QNEXA groups, whereas increases from baseline were observed for the placebo group.

Table 11. Alanine Transaminase and Aspartate Transaminase Changes From Baseline at Study Endpoint — Individual Studies OB-302 and OB-303 (ITT-LOCF Set)

Parameter Treatment	OB-302 Change at Week 56 (LOCF) [1]			OB-303 Change at Week 56 (LOCF) [2]		
	N	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value
Alanine transaminase, mU/mL						
Placebo	479	-0.7 (0.71)		939	-0.8 (0.60)	
QNEXA Low	230	-1.5 (0.95)	0.4931			
QNEXA Mid				475	-4.0 (0.79)	0.0002
QNEXA Top	486	-2.2 (0.71)	0.0921	964	-3.3 (0.59)	0.0004
Aspartate transaminase, mU/mL						
Placebo	478	0.7 (0.87)		940	0.9 (0.48)	
QNEXA Low	230	1.9 (1.17)	0.3578			
QNEXA Mid				475	-0.7 (0.63)	0.0286
QNEXA Top	486	-0.7 (0.87)	0.2018	964	-0.7 (0.47)	0.0050

1. Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender, as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
2. Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment, gender, and diabetic status as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT-LOCF=intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate; SE=standard error.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Examination of liver function test (LFT) values in subjects with elevated LFT values at baseline (upper quartile) indicated that subjects treated with QNEXA Mid and Top dose demonstrated significantly greater improvements in ALT values from baseline compared with subjects treated with placebo (**Table 12).**

Table 12. Alanine Transaminase Change From Baseline at Study Endpoint in Subjects in the Upper Quartile of Baseline Alanine Transaminase Distribution (ITT-LOCF, 1-Year Cohort)

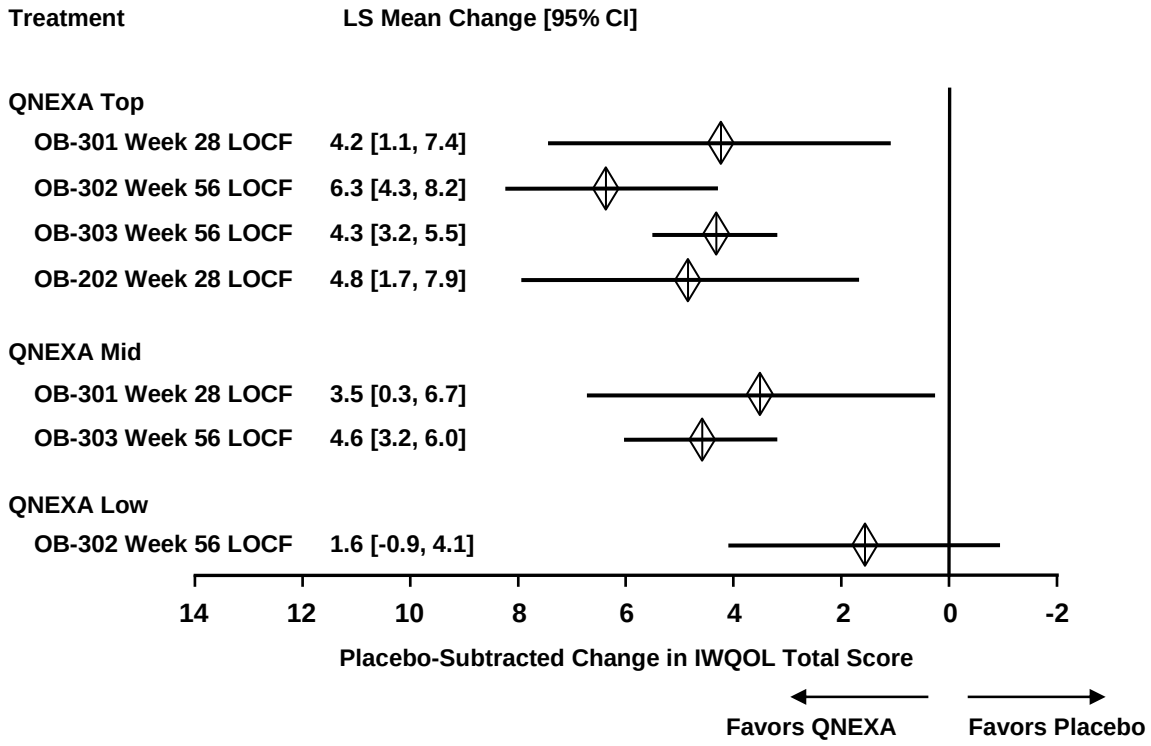
Time Point	Placebo (N=346)	QNEXA Low (N=38)	QNEXA Mid (N=142)	QNEXA Top (N=351)
Baseline, mU/mL [1]	50.0	49.1	51.8	50.5
Week 56, mU/mL [1]	41.3	37.1	35.0	34.6
Change from baseline to Week 56, mU/mL [2]	-9.2	-11.9	-16.7*	-16.3*

*p<0.0001 vs placebo.
1. Mean values.
2. Least-squares mean changes from baseline to Week 56 with LOCF.
Least-squares mean, SE, and p-value are from an analysis of covariance model with treatment, study, and gender as fixed effects and baseline as a covariate. All placebo comparisons are calculated as QNEXA minus placebo.
ITT-LOCF= intent-to-treat–last observation carried forward; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

4.3.7 Quality of Life

Subjects in the QNEXA clinical development program were evaluated with respect to changes in quality of life. The Impact of Weight on Quality of Life (IWQOL)-Lite© Questionnaire is a 31-item, self-administered instrument designed to evaluate the impact of excess weight on quality-of-life domains, including physical function, self-esteem, sexual life, public distress, and work **(Appendix 4, Section 12.4.2)**. The IWQOL Questionnaire was completed by subjects at screening, at Week 28, and at Week 56 or early termination. Scaled scores range from 1 to 100, with higher scores indicating better quality of life and composite scores reflecting overall performance within individual domains. Consistent and significant improvements from baseline in composite scores compared with placebo were observed in subjects treated with QNEXA Top dose across trials OB-202, OB-301, OB-302, and OB-303 **(Figure 24).** Improvements were also observed for QNEXA Mid and Low dose in the trials in which these doses were used. Changes of the greatest magnitude were observed in the domains of self-esteem and work function.

Figure 24. Placebo-Subtracted IWQOL Total Score Change From Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-202, OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI=confidence interval; ITT-LOCF=intent-to-treat–last observation carried forward; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

The Short Form (SF)-36 questionnaire **(Appendix 4, Section 12.4.4)** is an instrument designed to evaluate general health, and includes the domains of general health, physical functioning, physical role, bodily pain, vitality, social functioning, emotional role, and mental health. Scores range from 1 to 100, with higher scores indicating improved functional health and well-being. The SF-36 questionnaire was administered in study OB-303, wherein scores improved significantly from baseline vs placebo at Week 56 in physical domains (physical functioning, physical role, bodily pain, general health, and vitality) in subjects who were treated with QNEXA Mid dose or Top dose. Effects of QNEXA were neutral for social functioning as well as emotional role and mental health.

4.4 Additional Supportive Studies

4.4.1 Study OB-202

See **Section 4.3.4.3** above.

4.4.2 Study DM-230

Study DM-230 was a 28-week extension of study OB-202, which evaluated the long-term safety and efficacy of QNEXA in subjects with type 2 diabetes. Subjects who completed study OB-202 and opted to participate in this extension study remained on the double-blind treatment to which they were assigned in study OB-202. During the extension study, subjects in the active treatment group received QNEXA Top-dose capsules instead of the phentermine 15 mg capsules and topiramate 100 mg capsules administered separately in study OB-202.

Of the 210 subjects enrolled in study OB-202, 130 (61.9%) subjects continued into study DM-230. In total, 120 (92.3%) subjects completed the study, and 10 (7.7%) discontinued from the study. The reasons for discontinuation from the study were loss to follow-up (3.8%), poor compliance with the protocol (2.3%), AEs (0.8%), and lack of efficacy (0.8%).

Treatment with QNEXA Top dose resulted in a significantly greater percent weight loss from baseline at Week 56 (9.65% vs 2.58%, $p<0.0001$ vs placebo) and a higher proportion of subjects with ≥5% and ≥10% weight loss from baseline than placebo (65% vs 24% and 37% vs 9%,

respectively) at Week 56 with LOCF ($p \leq 0.0004$). Treatment with QNEXA Top dose also resulted in significant decreases from baseline in waist circumference (-8.14 vs -2.64 cm), SBP (-7.75 vs -2.12 mm Hg), HbA_{1c} (-1.61% vs -1.13%), fasting glucose (-43.24 vs -25.95 mg/dL), and fasting insulin (-2.09 vs -5.88 µIU/mL) at Week 56 with LOCF.

4.4.3 Study DM-231

Study DM-231 was designed as a 58-week, open-label extension of study DM-230 to evaluate the long-term safety and efficacy of QNEXA in subjects with type 2 diabetes. Subjects who completed study DM-230 and opted to participate in this extension study were treated with open-label QNEXA Top dose, 15/92 mg capsules. Subjects underwent a 4-week titration to reach the target dose of 15/92 mg (QNEXA Top dose). The extension study was terminated after 16 weeks based on input from the FDA that an open-label study would not be easily interpretable due to lack of a control group. The early termination was unrelated to safety or efficacy concerns.

4.4.4 Study OB-204

Study OB-204 was a randomized, double-blind, placebo-controlled, parallel-group study of QNEXA Top dose for the treatment of severe obstructive sleep apnea (OSA)/hypopnea syndrome in obese adults. The primary efficacy endpoint of the study was the change in apnea/hypoxia index (AHI) between baseline and Week 8 and Week 28 or ET in obese subjects with OSA. Overall, QNEXA demonstrated significant reductions from baseline in AHI events at Weeks 16 and 28 compared with placebo. Consistent with other Phase 2 and 3 studies, significant weight loss and improvements in multiple endpoints involving cardiometabolic risk factors were obtained. This study was not included as part of the NDA, but is included in this briefing document because of its relevance to the characterization assessment of both the efficacy and the tolerability of QNEXA**.**

5 INTEGRATED SAFETY OVERVIEW

The analysis population for safety summaries was the Safety set, defined as all randomized subjects who received at least one dose of study drug.

5.1 Subject Cohorts

Two analysis cohorts were integrated:

- **6-Month Cohort:** This cohort comprised all subjects from studies OB-202 and OB-301 and included the first 6 months of data for subjects in studies OB-302 and OB-303. The 6-month cutoff point for studies OB-302 and OB-303 was based on the date of the Week 28 visit. All data up to and including Week 28 were included from studies OB-302 and OB-303. Data from the phentermine 15 mg and topiramate 100 mg combination treatment group from study OB-202 were summarized under the Top-dose QNEXA treatment group in the integrated summaries.

- **1-Year Cohort:** This cohort comprised all subjects from studies OB-302 and OB-303 and all subjects who entered study DM-230, the 6-month extension to study OB-202. Data for subjects in OB-202 and DM-230 were combined to provide 1-year safety data.

5.2 Extent of Exposure

A total of 2943 subjects received at least 1 dose of QNEXA in the Phase 1 through Phase 3 clinical studies, and 1863 subjects received placebo **(Table 13)**.

Table 13. Estimated Exposure in Obesity Development Program

Study Type/Phase	Number of Subjects						
	Total Randomized	QNEXA Low	QNEXA Mid	QNEXA Top	QNEXA Other Doses	QNEXA (All Doses)	Placebo
Phase 1	606	88	142[a]	188[b]	142	490	56
Phase 2	490	0	45	200	--	200	200
Phase 3	4510	241	605	1615	--	2461	1617
Program Total	**5606**	329	792	2003	142	**3151**	1873

[a]Dose included 7.5/50 mg.
[b]Dose included 15/100 mg.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Extent of exposure to study drug was calculated as last dose date of double-blind study drug minus first dose date of double-blind study drug + 1. No adjustments to extent of exposure for dose interruptions or alternative dosing strategies were made. Extent of exposure was summarized with descriptive statistics by treatment group, combined QNEXA group, and overall for the 6-month and 1-year cohorts.

Table 14 summarizes extent of exposure to study drug for the 1-year cohort. Overall mean exposure to study drug was 286.1 days, and overall median exposure to study drug was 391.0 days. Mean exposure to study drug was similar for the treatment groups. In total, 1511 (65.2%) subjects on QNEXA and 862 (55.2%) subjects on placebo had >52 weeks of exposure to study drug.

A total of 2559 subjects were exposed to at least 1 dose of QNEXA in the 6-month cohort. Overall, mean exposure to study drug for the 6-month cohort was 159.3 days, and overall median exposure to study drug was 197.0 days. Mean exposure to study drug was similar for the treatment groups. In total, 1907 (74.5%) subjects on QNEXA and 1131 (65.8%) subjects on placebo had >24 weeks of exposure to study drug.

Table 14. Extent of Exposure to Study Drug (Safety Set, 1-Year Cohort)

Exposure	Placebo (N=1561)	QNEXA Low (N=240)	QNEXA Mid (N=498)	QNEXA Top (N=1580)
Extent of exposure, days				
N	1561	240	498	1580
Mean (SD)	268.8 (152.82)	282.2 (148.36)	308.2 (142.35)	296.8 (147.52)
Median	389.0	391.0	392.0	392.0
Specified exposure range, n (%)				
1 day to ≤2 weeks	71 (4.5)	12 (5.0)	18 (3.6)	67 (4.2)
>2 weeks to ≤4 weeks	49 (3.1)	6 (2.5)	23 (4.6)	86 (5.4)
>4 weeks to ≤8 weeks	102 (6.5)	7 (2.9)	20 (4.0)	82 (5.2)
>8 weeks to ≤12 weeks	106 (6.8)	14 (5.8)	20 (4.0)	56 (3.5)
>12 weeks to ≤16 weeks	70 (4.5)	17 (7.1)	12 (2.4)	40 (2.5)
>16 weeks to ≤20 weeks	70 (4.5)	8 (3.3)	10 (2.0)	28 (1.8)
>20 weeks to ≤24 weeks	50 (3.2)	9 (3.8)	6 (1.2)	27 (1.7)
>24 weeks to ≤28 weeks	54 (3.5)	8 (3.3)	11 (2.2)	33 (2.1)
>28 weeks to ≤32 weeks	26 (1.7)	2 (0.8)	4 (0.8)	28 (1.8)
>32 weeks to ≤36 weeks	33 (2.1)	0 (0.0)	5 (1.0)	24 (1.5)
>36 weeks to ≤40 weeks	18 (1.2)	7 (2.9)	6 (1.2)	23 (1.5)
>40 weeks to ≤44 weeks	16 (1.0)	3 (1.3)	7 (1.4)	16 (1.0)
>44 weeks to ≤48 weeks	15 (1.0)	3 (1.3)	6 (1.2)	25 (1.6)
>48 weeks to ≤52 weeks	19 (1.2)	1 (0.4)	3 (0.6)	24 (1.5)
>52 weeks to ≤56 weeks	398 (25.5)	55 (22.9)	167 (33.5)	458 (29.0)
>56 weeks	464 (29.7)	88 (36.7)	180 (36.1)	563 (35.6)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.3 Subject Disposition

Table 15 summarizes subject disposition for the 1-year cohort, which comprised 3884 subjects randomly assigned to treatment groups. Of the 3884 randomized subjects, 2342 (60.3%) completed all study visits on study drug and 1537 (39.6%) discontinued study drug. A higher percentage of subjects in the QNEXA treatment groups than in the placebo group completed the study on study drug (64.0% vs 54.8%). The most common reasons for discontinuation of study drug were AEs (12.7%), loss to follow-up (10.4%), and withdrawal of consent (10.2%). There was a dose-related increase in the percentage of subjects treated with QNEXA who discontinued study drug due to an AE; however, the overall retention rates were higher for all QNEXA treatment groups compared with placebo, with the highest rates shown for QNEXA Mid dose. Subject disposition results for the 6-month cohort were similar to that of the 1-year cohort.

Table 15. Subject Disposition (Randomized Set, 1-Year Cohort)

Disposition	Placebo (N=1563) n (%)	QNEXA Low (N=241) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1582) n (%)
Randomized	1563 (100.0)	241 (100.0)	498 (100.0)	1582 (100.0)
Completed all study visits	940 (60.1)	147 (61.0)	374 (75.1)	1141 (72.1)
Discontinued from study	623 (39.9)	94 (39.0)	124 (24.9)	441 (27.9)
Subject lost to follow-up	226 (14.5)	31 (12.9)	44 (8.8)	144 (9.1)
Subject withdrew consent	243 (15.5)	31 (12.9)	40 (8.0)	126 (8.0)
Adverse event	50 (3.2)	16 (6.6)	21 (4.2)	104 (6.6)
Lack of efficacy	47 (3.0)	3 (1.2)	1 (0.2)	3 (0.2)
Protocol noncompliance	14 (0.9)	4 (1.7)	0 (0.0)	16 (1.0)
Requirement for restricted medication	11 (0.7)	1 (0.4)	7 (1.4)	6 (0.4)
Pregnancy	2 (0.1)	1 (0.4)	1 (0.2)	16 (1.0)
Other	30 (1.9)	7 (2.9)	10 (2.0)	23 (1.5)
Completed all visits on study drug	857 (54.8)	138 (57.3)	344 (69.1)	1003 (63.4)
Discontinued study drug	704 (45.0)	102 (42.3)	154 (30.9)	577 (36.5)
Adverse event	132 (8.4)	28 (11.6)	58 (11.6)	276 (17.4)
Subject lost to follow-up	217 (13.9)	27 (11.2)	41 (8.2)	118 (7.5)
Subject withdrew consent	225 (14.4)	28 (11.6)	34 (6.8)	108 (6.8)
Lack of efficacy	63 (4.0)	6 (2.5)	3 (0.6)	11 (0.7)
Protocol noncompliance	18 (1.2)	5 (2.1)	3 (0.6)	14 (0.9)
Requirement for restricted medication	17 (1.1)	0 (0.0)	5 (1.0)	6 (0.4)
Pregnancy	2 (0.1)	1 (0.4)	1 (0.2)	15 (0.9)
Other	30 (1.9)	7 (2.9)	9 (1.8)	26 (1.6)
Safety set	1561 (99.9)	240 (99.6)	498 (100.0)	1580 (99.9)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Subjects may be counted in both study and study drug discontinuation sections.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.4 Adverse Events

5.4.1 Overview of Adverse Events

Table 16 provides an overall summary of AEs during the double-blind treatment period. A total of 3179 (82.0%) subjects in the 1-year cohort had a TEAE; 1704 (43.9%) subjects had a TEAE that was considered by the investigators to be related to the study drug. The overall incidence of TEAEs and study drug-related TEAEs was higher in all of the QNEXA treatment groups compared with the placebo group. Most TEAEs were mild or moderate in severity.

One subject in the integrated cohorts died. This subject was treated with placebo in Study OB-303 and died due to cardiopulmonary arrest. A detailed narrative of this event is provided in **Appendix 6**. No deaths occurred in any of the other clinical studies.

A total of 143 (3.7%) subjects had a serious adverse event (SAE), and 16 subjects (0.4%) had a drug-related SAE. The incidence of SAEs and drug-related SAEs was similar across the treatment groups.

A total of 494 (12.7%) subjects discontinued study drug due to an AE, while 353 (9.1%) subjects discontinued study drug due to a drug-related TEAE. The frequency of study drug discontinuations due to an AE or drug-related TEAE was higher in all of the QNEXA treatment groups compared with the placebo group.

Table 16. Overview of Adverse Events During the Double-Blind Treatment Period (Safety Set, 1-Year Cohort)

	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Subjects with TEAEs				
Any TEAE	1186 (76.0)	192 (80.0)	424 (85.1)	1377 (87.2)
Any drug-related TEAE	433 (27.7)	100 (41.7)	251 (50.4)	920 (58.2)
Maximum severity of TEAEs				
Mild	491 (31.5)	60 (25.0)	151 (30.3)	524 (33.2)
Moderate	561 (35.9)	107 (44.6)	218 (43.8)	656 (41.5)
Severe	134 (8.6)	25 (10.4)	55 (11.0)	197 (12.5)
Deaths	1 (0.1)	0	0	0
Subjects with SAEs				
Any SAE	55 (3.5)	6 (2.5)	15 (3.0)	67 (4.2)
Any treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)
Any drug-related SAE	6 (0.4)	1 (0.4)	1 (0.2)	8 (0.5)
Study drug discontinuations due to AEs/SAEs				
Any AE	132 (8.5)	28 (11.7)	58 (11.6)	276 (17.5)
Any TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)
Any drug-related TEAE	82 (5.3)	19 (7.9)	42 (8.4)	210 (13.3)
Any SAE	15 (1.0)	2 (0.8)	4 (0.8)	18 (1.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
AE=adverse event; QNEXA=fixed-dose combination of phentermine and topiramate; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

The overall incidence of TEAEs and study drug-related TEAEs with QNEXA treatment for the 6-month cohort was similar to that of the 1-year cohort. For the 6-month cohort, the overall incidence of TEAEs was 69.5% in the placebo group, 75.0% in the QNEXA Low-dose group, 80.0% in the QNEXA Mid-dose group, and 82.4% in the QNEXA Top-dose group.

No important differences were observed between the 1-year and 6-month cohorts in the types of TEAEs or incidence of specific TEAEs with QNEXA treatment, indicating that long-term treatment did not result in any new types of AEs or substantially increased rates of AEs.

5.4.2 Common Adverse Events

Table 17 shows the most common TEAEs (experienced by ≥2% of subjects in any treatment group) during the double-blind treatment period by system organ class (SOC) and preferred term for the 1-year cohort.

The incidences of the following TEAEs (preferred terms) were higher in one or more QNEXA groups compared with the placebo group: paresthesia, dry mouth, constipation, dysgeusia, insomnia, dizziness, depression, anxiety, hypoesthesia, alopecia, irritability, disturbance in attention, dry eye, hypokalemia, palpitations, thirst, and decreased appetite.

Table 17. Summary of Treatment-Emergent Adverse Events (≥2% of Subjects in Any Treatment Group) by System Organ Class and Preferred Term (Safety Set, 1-Year Cohort)

System Organ Class Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Infections and infestations	644 (41.3)	126 (52.5)	219 (44.0)	730 (46.2)
Upper respiratory tract infection	200 (12.8)	38 (15.8)	61 (12.2)	213 (13.5)
Nasopharyngitis	125 (8.0)	30 (12.5)	53 (10.6)	149 (9.4)
Sinusitis	98 (6.3)	18 (7.5)	34 (6.8)	123 (7.8)
Bronchitis	66 (4.2)	16 (6.7)	22 (4.4)	85 (5.4)
Influenza	69 (4.4)	18 (7.5)	23 (4.6)	69 (4.4)
Urinary tract infection	56 (3.6)	8 (3.3)	26 (5.2)	82 (5.2)
Gastroenteritis viral	45 (2.9)	8 (3.3)	13 (2.6)	43 (2.7)
Gastroenteritis	35 (2.2)	2 (0.8)	11 (2.2)	40 (2.5)
Gastrointestinal disorders	394 (25.2)	73 (30.4)	195 (39.2)	724 (45.8)
Constipation	96 (6.1)	19 (7.9)	75 (15.1)	255 (16.1)
Dry mouth	43 (2.8)	16 (6.7)	67 (13.5)	301 (19.1)
Nausea	69 (4.4)	14 (5.8)	18 (3.6)	114 (7.2)
Diarrhea	76 (4.9)	12 (5.0)	32 (6.4)	89 (5.6)
Dyspepsia	27 (1.7)	5 (2.1)	11 (2.2)	45 (2.8)
Gastroesophageal reflux disease	21 (1.3)	2 (0.8)	16 (3.2)	41 (2.6)
Abdominal pain	30 (1.9)	4 (1.7)	8 (1.6)	31 (2.0)
Vomiting	31 (2.0)	5 (2.1)	7 (1.4)	30 (1.9)
Paresthesia oral	4 (0.3)	1 (0.4)	3 (0.6)	35 (2.2)
Nervous system disorders	317 (20.3)	58 (24.2)	182 (36.5)	685 (43.4)
Paresthesia	30 (1.9)	10 (4.2)	68 (13.7)	315 (19.9)
Headache	145 (9.3)	25 (10.4)	35 (7.0)	167 (10.6)
Dizziness	53 (3.4)	7 (2.9)	36 (7.2)	136 (8.6)
Dysgeusia	17 (1.1)	3 (1.3)	37 (7.4)	149 (9.4)
Hypoesthesia	19 (1.2)	2 (0.8)	18 (3.6)	58 (3.7)
Disturbance in attention	10 (0.6)	1 (0.4)	10 (2.0)	55 (3.5)
Musculoskeletal and connective tissue disorders	319 (20.4)	48 (20.0)	107 (21.5)	340 (21.5)
Back pain	80 (5.1)	13 (5.4)	28 (5.6)	105 (6.6)
Arthralgia	75 (4.8)	11 (4.6)	23 (4.6)	68 (4.3)
Pain in extremity	44 (2.8)	5 (2.1)	15 (3.0)	48 (3.0)
Muscle spasms	35 (2.2)	7 (2.9)	14 (2.8)	46 (2.9)
Musculoskeletal pain	18 (1.2)	2 (0.8)	15 (3.0)	25 (1.6)
Neck pain	20 (1.3)	3 (1.3)	11 (2.2)	19 (1.2)
Psychiatric disorders	172 (11.0)	34 (14.2)	74 (14.9)	362 (22.9)
Insomnia	74 (4.7)	12 (5.0)	29 (5.8)	148 (9.4)
Depression	35 (2.2)	8 (3.3)	14 (2.8)	68 (4.3)
Anxiety	29 (1.9)	7 (2.9)	9 (1.8)	65 (4.1)
General disorders and administration site conditions	200 (12.8)	32 (13.3)	83 (16.7)	303 (19.2)
Fatigue	67 (4.3)	12 (5.0)	22 (4.4)	93 (5.9)
Irritability	11 (0.7)	4 (1.7)	13 (2.6)	58 (3.7)
Edema peripheral	45 (2.9)	2 (0.8)	6 (1.2)	29 (1.8)

Table 17. Summary of Treatment-Emergent Adverse Events (≥2% of Subjects in Any Treatment Group) by System Organ Class and Preferred Term (Safety Set, 1-Year Cohort)

System Organ Class Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Thirst	11 (0.7)	5 (2.1)	9 (1.8)	31 (2.0)
Chest discomfort	7 (0.4)	5 (2.1)	1 (0.2)	14 (0.9)
Respiratory, thoracic, and mediastinal disorders	193 (12.4)	33 (13.8)	64 (12.9)	254 (16.1)
Cough	54 (3.5)	8 (3.3)	19 (3.8)	76 (4.8)
Sinus congestion	32 (2.0)	6 (2.5)	13 (2.6)	31 (2.0)
Pharyngolaryngeal pain	32 (2.0)	6 (2.5)	6 (1.2)	36 (2.3)
Nasal congestion	22 (1.4)	4 (1.7)	6 (1.2)	31 (2.0)
Asthma	18 (1.2)	3 (1.3)	10 (2.0)	15 (0.9)
Eye disorders	163 (10.4)	32 (13.3)	72 (14.5)	236 (14.9)
Vision blurred	55 (3.5)	15 (6.3)	20 (4.0)	86 (5.4)
Eye pain	22 (1.4)	5 (2.1)	11 (2.2)	35 (2.2)
Dry eye	12 (0.8)	2 (0.8)	7 (1.4)	39 (2.5)
Injury, poisoning, and procedural complications	193 (12.4)	19 (7.9)	77 (15.5)	197 (12.5)
Procedural pain	26 (1.7)	5 (2.1)	12 (2.4)	30 (1.9)
Joint sprain	23 (1.5)	0 (0.0)	10 (2.0)	16 (1.0)
Skin and subcutaneous tissue disorders	145 (9.3)	17 (7.1)	65 (13.1)	244 (15.4)
Rash	34 (2.2)	4 (1.7)	10 (2.0)	41 (2.6)
Alopecia	11 (0.7)	5 (2.1)	13 (2.6)	59 (3.7)
Metabolism and nutrition disorders	121 (7.8)	12 (5.0)	50 (10.0)	158 (10.0)
Hypokalemia	6 (0.4)	1 (0.4)	7 (1.4)	40 (2.5)
Decreased appetite	10 (0.6)	5 (2.1)	9 (1.8)	23 (1.5)
Reproductive system and breast disorders	62 (4.0)	15 (6.3)	25 (5.0)	114 (7.2)
Dysmenorrhea	3 (0.2)	5 (2.1)	2 (0.4)	13 (0.8)
Vascular disorders	91 (5.8)	10 (4.2)	27 (5.4)	76 (4.8)
Hypertension	56 (3.6)	6 (2.5)	14 (2.8)	25 (1.6)
Cardiac disorders	28 (1.8)	4 (1.7)	19 (3.8)	56 (3.5)
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)
Immune system disorders	45 (2.9)	5 (2.1)	10 (2.0)	31 (2.0)
Seasonal allergy	35 (2.2)	3 (1.3)	10 (2.0)	27 (1.7)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.4.3 Adverse Events by Maximum Severity

Most TEAEs were mild or moderate in severity for subjects in the 1-year cohort.
The distributions of TEAEs by maximum severity were similar for the placebo group and QNEXA Mid- and Top-dose groups (see **Table 16** above). In total, 411 (10.6%) subjects had a severe TEAE: 134 (8.6%) subjects in the placebo group, 25 (10.4%) subjects in the QNEXA Low-dose group, 55 (11.0%) subjects in the QNEXA Mid-dose group, and 197 (12.5%) subjects in the QNEXA Top-dose group.

Table 18 summarizes the severe TEAEs that occurred in ≥0.5% of subjects in any treatment group during the double-blind treatment period by preferred term for the 1-year cohort. Specific severe psychiatric TEAEs were experienced by fewer than 0.5% of subjects in any treatment group.

Table 18. Summary of Severe Treatment-Emergent Adverse Events (≥0.5% of Subjects in Any Treatment Group) by Preferred Term (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Severe TEAEs	134 (8.6)	25 (10.4)	55 (11.0)	197 (12.5)
Dry mouth	1 (0.1)	1 (0.4)	0 (0.0)	17 (1.1)
Headache	7 (0.4)	1 (0.4)	3 (0.6)	14 (0.9)
Back pain	3 (0.2)	1 (0.4)	3 (0.6)	9 (0.6)
Constipation	2 (0.1)	0 (0.0)	3 (0.6)	9 (0.6)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)
Toothache	0 (0.0)	2 (0.8)	1 (0.2)	1 (0.1)
Cholelithiasis	6 (0.4)	2 (0.8)	0 (0.0)	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.4.4 Targeted Medical Events

Based on the known adverse effects of phentermine HCl or topiramate, as reported in the product labels or literature, and on regulatory questions regarding effects of the drugs on particular

systems, certain classes of AEs were specified as targeted medical events (TME). For example, the Depression (standardized Medical Dictionary for Regulatory Activities [MedDRA] query [SMQ]) subclass comprises reports of affect lability, apathy, crying, depressed mood, depression, dysthymic disorder, mood altered, and tearfulness. **Table 19** summarizes targeted medical events that occurred in the 1-year cohort. The types and frequencies of targeted medical events were similar in the 6-month cohort.

Table 19. Proportion of Subjects With Treatment-Emergent Adverse Events Categorized as Targeted Medical Events by Class and Subclass (Safety Set, 1-Year Cohort)

TME Class TME Subclass	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Psychiatric disorders class				
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Depression (SMQ) subclass [1]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0	0
Cognitive disorders class				
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Language subclass	1 (0.1)	0	3 (0.6)	19 (1.2)
Other cognitive disorders NOS subclass	5 (0.3)	2 (0.8)	5 (1.0)	28 (1.8)
Ophthalmic disorders class				
Ophthalmic disorders subclass	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)
Menstrual disorders class				
Menstrual disorders subclass	27 (1.7)	5 (2.1)	8 (1.6)	38 (2.4)
Psychomotor disorders class				
Psychomotor disorders subclass	1 (0.1)	0	2 (0.4)	12 (0.8)

1. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
NOS=not otherwise specified; QNEXA=fixed-dose combination of phentermine and topiramate; SMQ=standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME=targeted medical event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In the Psychiatric Disorders class, the incidence of TEAEs in the sleep disorders and depression (SMQ) subclasses was higher in the QNEXA Top-dose group than in the other treatment groups. The incidence of TEAEs in the anxiety subclass was higher in all QNEXA groups compared with the placebo group. In the suicide/self-injury (SMQ) subclass, two events were reported: one

in the placebo group and one in the QNEXA Low-dose group. Events in this class are further discussed in **Section 7.1**.

In the Cognitive Disorders class, the incidence of TEAEs in the attention and memory impairment subclasses was higher in the QNEXA Mid- and Top-dose groups than in the QNEXA Low-dose and placebo groups. The incidence of TEAEs in the language and other cognitive disorders subclasses was low overall, but higher in the QNEXA Top-dose group compared with the other treatment groups. Events in this class are further discussed in **Section 7.2**.

The incidence of TEAEs in the Ophthalmic Disorders and Menstrual Disorders classes was low (≤2.5%) and similar across the treatment groups.

The incidence of TEAEs in the Psychomotor Disorders class was low (<1%) overall, but higher in the QNEXA Top-dose group compared with the other treatment groups. No TEAEs were reported in the drug abuse (SMQ) or drug withdrawal (SMQ) subclass in any of the treatment groups.

5.4.4.1 Severity of Targeted Medical Events

Table 20 summarizes the subclasses of targeted medical events by maximum severity for the 1-year cohort. Most of the TEAEs that were categorized as targeted medical events were mild in severity.

Table 20. Summary of Treatment-Emergent Targeted Medical Events at the Subclass Level by Maximum Severity (Safety Set, 1-Year Cohort)

TME Subclass Maximum Severity	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Mild	58 (3.7)	9 (3.8)	19 (3.8)	98 (6.2)
Moderate	29 (1.9)	7 (2.9)	15 (3.0)	65 (4.1)
Severe	2 (0.1)	0 (0.0)	0 (0.0)	7 (0.4)
Depression (SMQ) subclass [1]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Mild	24 (1.5)	8 (3.3)	13 (2.6)	67 (4.2)
Moderate	27 (1.7)	3 (1.3)	4 (0.8)	47 (3.0)
Severe	2 (0.1)	1 (0.4)	2 (0.4)	7 (0.4)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Mild	23 (1.5)	7 (2.9)	11 (2.2)	68 (4.3)
Moderate	15 (1.0)	2 (0.8)	11 (2.2)	48 (3.0)
Severe	3 (0.2)	2 (0.8)	2 (0.4)	9 (0.6)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Mild	5 (0.3)	1 (0.4)	8 (1.6)	37 (2.3)
Moderate	4 (0.3)	0 (0.0)	2 (0.4)	18 (1.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Mild	8 (0.5)	2 (0.8)	9 (1.8)	31 (2.0)
Moderate	2 (0.1)	0 (0.0)	0 (0.0)	8 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Language subclass	1 (0.1)	0 (0.0)	3 (0.6)	19 (1.2)
Mild	1 (0.1)	0 (0.0)	2 (0.4)	12 (0.8)
Moderate	0 (0.0)	0 (0.0)	1 (0.2)	6 (0.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Other cognitive disorders NOS subclass	5 (0.3)	2 (0.8)	5 (1.0)	28 (1.8)
Mild	2 (0.1)	0 (0.0)	3 (0.6)	17 (1.1)
Moderate	3 (0.2)	2 (0.8)	1 (0.2)	10 (0.6)
Severe	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Ophthalmic disorders subclass	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)
Mild	18 (1.2)	3 (1.3)	9 (1.8)	31 (2.0)
Moderate	7 (0.4)	3 (1.3)	3 (0.6)	8 (0.5)
Severe	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual disorders subclass	27 (1.7)	5 (2.1)	8 (1.6)	38 (2.4)
Mild	15 (1.0)	5 (2.1)	6 (1.2)	24 (1.5)
Moderate	12 (0.8)	0 (0.0)	2 (0.4)	13 (0.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychomotor disorders subclass	1 (0.1)	0 (0.0)	2 (0.4)	12 (0.8)
Mild	1 (0.1)	0 (0.0)	1 (0.2)	7 (0.4)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
Severe	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
NOS=not otherwise specified; QNEXA=fixed-dose combination of phentermine and topiramate; SMQ=standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME=targeted medical event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

The incidences of TEAEs categorized as targeted medical events for the 6-month cohort were similar to those for the 1-year cohort.

5.4.5 Other Serious Adverse Events

Table 21 summarizes treatment-emergent SAEs in the 1-year cohort by SOC. The incidence of treatment-emergent SAE was low and similar across the treatment groups. No specific event terms were reported as SAEs by >0.5% of subjects in any treatment group.

Table 21. Summary of Treatment-Emergent Serious Adverse Events by System Organ Class (Safety Set, 1-Year Cohort)

System Organ Class Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Any treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)
Infections and infestations	2 (0.1)	2 (0.8)	3 (0.6)	11 (0.7)
Cardiac disorders	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8 (0.5)	0 (0.0)	1 (0.2)	6 (0.4)
Hepatobiliary disorders	5 (0.3)	1 (0.4)	0 (0.0)	7 (0.4)
Musculoskeletal and connective tissue disorders	4 (0.3)	0 (0.0)	0 (0.0)	6 (0.4)
Vascular disorders	2 (0.1)	2 (0.8)	1 (0.2)	4 (0.3)
Gastrointestinal disorders	5 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)
General disorders and administration site conditions	7 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	4 (0.3)	0 (0.0)	2 (0.4)	2 (0.1)
Respiratory, thoracic, and mediastinal disorders	3 (0.2)	0 (0.0)	2 (0.4)	2 (0.1)
Reproductive system and breast disorders	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)
Renal and urinary disorders	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)
Injury, poisoning, and procedural complications	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA=fixed-dose combination of phentermine and topiramate; SAE=serious adverse event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.4.6 Discontinuations From Study Drug Due to Adverse Events

Table 22 summarizes the TEAEs that resulted in study drug discontinuation in ≥1% of subjects in any treatment group. Overall, 490 (12.6%) subjects had a TEAE that resulted in study drug discontinuation. The frequency of these events was generally higher in all QNEXA treatment groups compared with placebo, with the highest incidence occurring in the QNEXA Top-dose group.

Table 22. Study Drug Discontinuations Due to Treatment-Emergent Adverse Events Occurring in ≥1% of Subjects in Any Treatment Group (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Discontinuation due to TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)
Insomnia	6 (0.4)	0 (0.0)	2 (0.4)	25 (1.6)
Depression	3 (0.2)	0 (0.0)	4 (0.8)	21 (1.3)
Paresthesia	0 (0.0)	1 (0.4)	5 (1.0)	18 (1.1)
Irritability	1 (0.1)	2 (0.8)	4 (0.8)	18 (1.1)
Anxiety	4 (0.3)	0 (0.0)	1 (0.2)	17 (1.1)
Dizziness	3 (0.2)	1 (0.4)	6 (1.2)	12 (0.8)
Blurred vision	8 (0.5)	5 (2.1)	4 (0.8)	11 (0.7)
Headache	10 (0.6)	4 (1.7)	1 (0.2)	13 (0.8)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
QNEXA=fixed-dose combination of phentermine and topiramate; TEAE=treatment-emergent adverse event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.5 Clinical Laboratory Evaluations

Overall, no differences were noted between the QNEXA treatment groups and the placebo group in terms of the incidence of serious laboratory-related AEs or study drug discontinuations due to a laboratory-related AE. In the 1-year cohort, three subjects experienced a serious laboratory-related TEAE: one subject in the QNEXA Top-dose group had a SAE of abnormal LFT, one subject in the placebo group had a SAE of hypokalemia, and one subject in the placebo group had a SAE of hyponatremia. Eighteen (0.5%) subjects discontinued study drug due to a TEAE in the Investigations SOC: 8 (0.5%) subjects in the placebo group, 2 (0.4%) in the QNEXA Mid-dose group, and 8 (0.5%) in the QNEXA Top-dose group.

Table 23 shows the mean change in selected laboratory parameters from baseline to endpoint for the 1-year cohort. All of the treatment groups had mean decreases in ALT and alkaline phosphatase (ALP) from baseline; the mean decreases in ALT were greater for the QNEXA Mid- and Top-dose groups than for the QNEXA Low-dose and placebo groups. The QNEXA Mid- and Top-dose groups had mean decreases in AST from baseline, whereas the QNEXA Low-dose and placebo groups had mean increases in AST. All QNEXA treatment groups showed mean decreases in serum bicarbonate from baseline; the placebo group had a small mean increase in serum bicarbonate. Other than the mean decreases in ALT and AST for the QNEXA Mid- and Top-dose groups, no clinically meaningful differences were noted among the treatment groups in mean changes in safety laboratory parameters.

Table 23. Selected Laboratory Parameters Changes From Baseline to Study Endpoint (Safety Set, 1-Year Cohort)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Alanine transaminase, mU/mL				
n [1]	1473	230	475	1525
Baseline [2], mean (SD)	29.4 (15.34)	25.7 (12.99)	31.5 (16.49)	29.8 (15.48)
Endpoint [3], mean (SD)	27.7 (16.88)	23.6 (13.84)	26.3 (14.60)	25.6 (18.48)
Mean change (SD)	-1.7 (14.29)	-2.1 (13.04)	-5.2 (15.92)	-4.2 (19.26)
p-value [4]	<0.0001	0.0134	<0.0001	<0.0001
Aspartate transaminase, mU/mL				
n [1]	1473	230	475	1525
Baseline [2], mean (SD)	23.8 (8.78)	21.4 (7.37)	25.1 (9.23)	24.1 (8.65)
Endpoint [3], mean (SD)	24.2 (12.00)	23.3 (35.38)	23.8 (18.04)	22.6 (9.41)
Mean change (SD)	0.4 (10.78)	1.9 (35.56)	-1.3 (17.83)	-1.5 (10.20)
p-value [4]	0.1953	0.4165	0.1159	<0.0001
Creatinine, mg/dL				
n [1]	1475	230	475	1525
Baseline [2], mean (SD)	0.86 (0.174)	0.84 (0.156)	0.86 (0.177)	0.85 (0.170)
Endpoint [3], mean (SD)	0.84 (0.176)	0.84 (0.165)	0.89 (0.188)	0.89 (0.183)
Mean change (SD)	-0.02 (0.101)	0.00 (0.094)	0.03 (0.104)	0.04 (0.111)
p-value [4]	<0.0001	0.9944	<0.0001	<0.0001
Alkaline phosphatase, mU/mL				
n [1]	1475	230	475	1525
Baseline [2], mean (SD)	79.8 (22.27)	79.7 (20.59)	78.7 (20.71)	79.0 (20.96)
Endpoint [3], mean (SD)	77.6 (22.21)	78.0 (20.90)	76.1 (21.78)	76.5 (21.79)
Mean change (SD)	-2.2 (12.49)	-1.7 (12.01)	-2.6 (13.97)	-2.5 (12.97)
p-value [4]	<0.0001	0.0295	<0.0001	<0.0001
Total bilirubin, mg/dL				
n [1]	1475	230	475	1525
Baseline [2], mean (SD)	0.45 (0.197)	0.43 (0.216)	0.46 (0.208)	0.45 (0.204)
Endpoint [3], mean (SD)	0.48 (0.210)	0.48 (0.215)	0.49 (0.226)	0.48 (0.211)
Mean change (SD)	0.03 (0.161)	0.05 (0.143)	0.03 (0.176)	0.03 (0.169)
p-value [4]	<0.0001	<0.0001	<0.0001	<0.0001
Bicarbonate, mEq/L				
n [1]	1475	230	475	1525
Baseline [2], mean (SD)	26.2 (2.52)	26.4 (2.54)	26.1 (2.72)	26.3 (2.49)
Endpoint [3], mean (SD)	26.4 (2.77)	24.9 (2.56)	25.8 (2.91)	25.0 (2.96)
Mean change (SD)	0.2 (3.09)	-1.6 (3.01)	-0.3 (3.12)	-1.3 (3.19)
p-value [4]	0.0152	<0.0001	0.0605	<0.0001
Potassium, mEq/L				
n [1]	1474	230	475	1523
Baseline [2], mean (SD)	4.28 (0.386)	4.27 (0.357)	4.26 (0.396)	4.27 (0.390)
Endpoint [3], mean (SD)	4.37 (0.409)	4.33 (0.382)	4.27 (0.415)	4.27 (0.434)
Mean change (SD)	0.09 (0.416)	0.07 (0.378)	0.02 (0.414)	0.01 (0.456)
p-value [4]	<0.0001	0.0077	0.3245	0.6410
Blood urea nitrogen, mg/dL				
n [1]	1475	230	475	1525
Baseline [2], mean (SD)	14.2 (4.12)	13.0 (3.47)	14.8 (4.04)	14.1 (3.82)
Endpoint [3], mean (SD)	14.3 (4.43)	13.1 (3.75)	15.9 (4.61)	15.0 (4.40)

Table 23. Selected Laboratory Parameters Changes From Baseline to Study Endpoint (Safety Set, 1-Year Cohort)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Mean change (SD)	0.2 (3.63)	0.1 (3.42)	1.2 (4.04)	0.8 (3.64)
p-value [4]	0.1183	0.5373	<0.0001	<0.0001
Hemoglobin, g/dL				
n [1]	1212	195	442	1392
Baseline [2], mean (SD)	14.0 (1.32)	13.9 (1.20)	14.1 (1.33)	14.0 (1.25)
Endpoint [3], mean (SD)	13.8 (1.34)	13.9 (1.24)	14.0 (1.38)	13.8 (1.33)
Mean change (SD)	-0.2 (0.75)	0.0 (0.75)	-0.1 (0.76)	-0.1 (0.80)
p-value [4]	<0.0001	0.5407	0.0005	<0.0001
Hematocrit, %				
n [1]	1212	195	442	1392
Baseline [2], mean (SD)	41.6 (3.70)	41.1 (3.35)	42.0 (3.74)	41.4 (3.54)
Endpoint [3], mean (SD)	41.2 (3.76)	41.2 (3.62)	41.6 (3.87)	41.2 (3.78)
Mean change (SD)	-0.4 (2.36)	0.1 (2.24)	-0.4 (2.40)	-0.3 (2.51)
p-value [4]	<0.0001	0.5239	0.0010	<0.0001

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. n is the number of subjects with baseline and endpoint measurements.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
3. Endpoint is the last available measurement obtained during the double-blind treatment period.
4. Two-sided p-value is from t-test testing whether change is equal to 0 within the treatment group.
QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

The clinical laboratory evaluations for the 6-month cohort also showed no adverse effects of QNEXA treatment on safety laboratory parameters.

Table 24 summarizes the incidence of elevations in liver function tests during the double-blind treatment period for the 1-year cohort based on categories as specified in the FDA Guidance on drug-induced liver injury (Food and Drug Administration 2009). The rates of significant elevations in liver function tests were low and similar across the treatment groups. No differences were observed relative to placebo in any QNEXA treatment groups. Similar results were observed for the 6-month cohort.

Two subjects had elevations in liver transaminases that met the criteria of Hy's law (i.e., >3 × upper limit of normal [ULN] AST or ALT plus >2 × ULN total bilirubin). In both of these subjects, elevations in transaminases occurred concurrently with SAEs of cholelithiasis, which resolved with treatment. These two events are described below:

- One subject who received placebo in study OB-302 was hospitalized with severe right upper quadrant abdominal pain associated with nausea, fever, and chills. Laboratory test results upon admission showed AP 234 IU/L, total bilirubin 4.8 mg/dL, ALT 232 IU/L, AST 88 IU/L, and white blood cell 17 K/µL. An abdominal ultrasound revealed no gallstones, minimal sludge, thickened gallbladder wall, mild hepatomegaly, and mild splenomegaly. An endoscopic procedure showed mildly dilated common bile duct, and the cystic duct was filled with stones. Biopsy results of the gallbladder revealed a diagnosis of chronic cholecystitis with acute exacerbation and eosinophils. The subject was treated for this event, and he recovered from the event 2 days later and was discharged from the hospital.

- One subject who received QNEXA Top-dose treatment in study OB-202 was hospitalized with cholelithiasis. After 4 months on study, the subject complained of bloating, pressure, and feelings of hunger that did not resolve with eating. Laboratory values showed white blood cell count of 12.7 K/µL, lipase 2203 IU/L, total bilirubin 2.9 mg/dL, AST 494 IU/L, and ALT 357 IU/L, all of which were elevated. An abdominal ultrasound revealed intra and extrahepatic biliary and pancreatic duct dilation, numerous gallstones and sludge and a hypoechoic pancreas. An endoscopic retrograde cholangiopancreatography and cholecystectomy were performed. The subject was treated for this event, and she recovered from the event on the same day and was discharged from the hospital. The investigator assessed the worsening cholelithiasis as moderate in severity and as not related to study medication.

Both subjects remained on study drug, and the events resolved with no sequelae.

Table 24. Summary of Significant Elevations in Liver Function Tests During Double-Blind Treatment (Safety Set, 1-Year Cohort)

Liver Function Test Category	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
ALT elevation				
>3 × ULN	15 (1.0)	2 (0.8)	3 (0.6)	16 (1.0)
>5 × ULN	5 (0.3)	0 (0.0)	1 (0.2)	6 (0.4)
>10 × ULN	1 (0.1)	0 (0.0)	1 (0.2)	3 (0.2)
>20 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST elevation				
>3 × ULN	12 (0.8)	2 (0.8)	2 (0.4)	5 (0.3)
>5 × ULN	4 (0.3)	2 (0.8)	2 (0.4)	3 (0.2)
>10 × ULN	1 (0.1)	1 (0.4)	1 (0.2)	1 (0.1)
>20 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin elevation				
>1.5 × ULN	12 (0.8)	2 (0.8)	4 (0.8)	12 (0.8)
>2 × ULN	3 (0.2)	1 (0.4)	0 (0.0)	1 (0.1)
Alkaline phosphatase elevation				
>1.5 × ULN	10 (0.6)	0 (0.0)	2 (0.4)	5 (0.3)
ALT or AST with total bilirubin elevation				
ALT or AST >3 × ULN and total bilirubin >1.5 × ULN	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
ALT or AST >3 × ULN and total bilirubin >2 × ULN	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
All measurements taken during the double-blind treatment period are considered.
ALT=alanine transaminase; AST=aspartate transaminase; QNEXA=fixed-dose combination of phentermine and topiramate; ULN=upper limit of normal.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Table 25 provides a summary of changes in serum bicarbonate, serum potassium, and serum creatinine during the double-blind treatment period for the 1-year cohort. The percentage of subjects with serum bicarbonate values <17 mEq/L at any time point during the double-blind treatment period was higher in the QNEXA treatment groups than in the placebo group, although no dose-related trend was evident. No subjects in the placebo or QNEXA Low-dose groups and few subjects in the QNEXA Mid- and Top-dose groups had serum potassium <3.0 mmol/L concurrent with a decrease of >0.5 mmol/L from baseline. Similarly, no subjects in the placebo, QNEXA Low-dose, or QNEXA Mid-dose groups, and not more than 2 (0.1%) subjects in the QNEXA Top-dose group had increased serum creatinine >100% of baseline at the final visit, during the titration phase, or during the maintenance phase.

Table 25. Summary of Changes in Selected Laboratory Parameters During the Double-Blind Treatment Period (Safety Set, 1-Year Cohort)

Change in Chemistry Parameter Time Point	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Serum bicarbonate <17 mEq/L				
At final visit	1 (0.1)	2 (0.8)	0	7 (0.4)
During titration phase	1 (0.1)	0	3 (0.6)	12 (0.8)
During maintenance phase	3 (0.2)	4 (1.7)	6 (1.2)	23 (1.5)
Persistence	1 (0.1)	2 (0.8)	1 (0.2)	11 (0.7)
Serum potassium <3.0 mmol/L and decrease from baseline >0.5 mmol/L				
At final visit	0	0	0	2 (0.1)
During titration phase	0	0	1 (0.2)	4 (0.3)
During maintenance phase	0	0	1 (0.2)	7 (0.4)
Persistence	0	0	1 (0.2)	2 (0.1)
Serum creatinine increase >100% from baseline				
At final visit	0	0	0	1 (0.1)
During titration phase	0	0	0	2 (0.1)
During maintenance phase	0	0	0	1 (0.1)
Persistence	0	0	0	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
All measurements taken during the double-blind treatment period are considered.
The titration phase is the period of time from the first dose of double-blind study drug up to and including the Week 4 visit date. For subjects continuing beyond Week 4, the Week 4 visit date is the cutoff. The maintenance phase is defined as the period of time from the Week 4 visit date to the date of completion or early termination from the study.
Persistence is defined as occurring at two consecutive visits or being present at the final visit.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Table 26 shows the risk of serum bicarbonate reductions in the presence or absence of metformin. Overall, there was no increased risk of metabolic acidosis when metformin was co-administered with QNEXA.

Table 26. Risk of Serum Bicarbonate Reductions in Presence or Absence of Metformin

Treatment group Subgroup	Placebo n (%)	QNEXA Total n (%)
Subjects taking metformin at any time, n [1]	**184**	**246**
Persistent bicarbonate <21 mEq/L	6 (3.3)	28 (11.4)
Persistent bicarbonate <17 mEq/L	0 (0.0)	2 (0.8)
Subjects not taking metformin, n	**1377**	**2072**
Persistent bicarbonate <21 mEq/L	26 (1.9)	225 (10.9)
Persistent bicarbonate <17 mEq/L	1 (0.1)	13 (0.6)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. Counts for persistence represent subjects who were taking metformin within 30 days of the first abnormal bicarbonate value.
QNEXA=fixed-dose combination of phentermine and topiramate.

Table 27 shows the incidence of reduced serum potassium in the presence or absence of non-potassium-sparing diuretics. Overall, low rates of mild hypokalemia were observed in subjects taking non-potassium-sparing diuretics.

Table 27. Serum Potassium Reduction in Presence or Absence of Non-Potassium-Sparing Diuretics in Phase 3 Studies

Treatment group Subgroup	Placebo n (%)	QNEXA Total n (%)
Subjects taking non-potassium-sparing diuretics, n	**476**	**742**
Persistent potassium <3.5 mmol/L [1]	14 (2.9)	85 (11.5)
Potassium <3.0 and >0.5 mmol /L from baseline	0 (0.0)	12 (1.6)
Persistent potassium <3.0 mmol/L [1]	0 (0.0)	4 (0.5)
Subjects not taking non-potassium-sparing diuretics, n	**1085**	**1576**
Persistent potassium <3.5 mmol/L [1]	3 (0.3)	11 (0.7)
Potassium <3.0 and >0.5 mmol /L from baseline	0 (0.0)	0 (0.0)
Persistent potassium <3.0 mmol/L [1]	0 (0.0)	0 (0.0)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. Less than 3.5 mEq/L at 2 consecutive measurements or at final visit.
QNEXA=fixed-dose combination of phentermine and topiramate.

5.6 Additional Safety Assessments

5.6.1 Pregnancy Outcomes

Table 28 summarizes the number of pregnancies that occurred during the QNEXA clinical development program. Overall, 34 pregnancies were reported: 29 in subjects on active treatment and 5 in subjects on placebo. All births were associated with healthy normal newborns and 6 other pregnancies resulted in spontaneous miscarriages. To date, none of these pregnancies has been associated with adverse outcomes, except the ectopic pregnancy that was reported as an SAE.

Table 28. Pregnancy Outcomes by Treatment Group

Outcomes, n	Placebo	QNEXA [1]	PHEN 15 mg	TPM 46 mg	TPM 92 mg	QNEXA Low	QNEXA Mid	QNEXA Top	TOTAL[2]
Pregnancies	**5**	**3**	**2**	**1**	**2**	**1**	**3**	**17**	**34**
Births with congenital abnormality	0	0	0	0	0	0	0	0	0
Healthy live births	3	1	1	1	1	1	2	9	19
Spontaneous abortions	1	1	0	0	0	0	0	4	6
Elective abortions	1	0	1	0	0	0	0	4	6
Ectopic pregnancies	0	1	0	0	0	0	0	0	1
Unconfirmed pregnancy	0	0	0	0	1	0	0	0	1
Lost to follow-up	0	0	0	0	0	0	1	0	1

Data from studies OB-118, OB-205, OB-301, OB-302, OB-303 and OB-305 are included.
1. Unable to determine dose due to study design.
2. As of June 3, 2010.
PHEN=phentermine; QNEXA=fixed-dose combination of phentermine and topiramate; TPM=topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

5.6.2 Body Composition Outcomes

Efficacy results for body composition are presented in **Section 4.3.3**. Overall, no adverse changes were observed.

5.7 Summary of Safety

The integrated analysis of safety was based on 3879 subjects enrolled in the three pivotal Phase 3 studies (OB-301, OB-302, and OB-303) and two supportive Phase 2 studies (OB-202 and DM-230). The safety population was diverse in age, race, and sex, representing the broader population of obese and overweight subjects with multiple co-morbidities, including depression. Most side effects were mild to moderate in severity, manageable and reversible, and consistent with the known safety profile of phentermine HCl and topiramate. No unexpected toxicity was observed. The integrated safety analysis demonstrated that QNEXA is safe and generally well tolerated in the intended population over a period of 6 months to 1 year at all tested dose levels. No clinically meaningful effects on cognitive function, anxiety, depression, or cardiovascular function were observed over 1 year.

The safety profile of QNEXA was similar in the 6-month and 1-year cohorts. Most TEAEs were observed during the first few months on study, and no new safety signals or substantially increased frequency of TEAEs emerged with continued therapy. In the 6-month and 1-year cohorts, the most frequently reported TEAEs associated with QNEXA were paresthesia, dry mouth, constipation, upper respiratory tract infection, nasopharyngitis, headache, and dysgeusia. The incidences of paresthesia, dry mouth, constipation, dysgeusia, insomnia, dizziness, hypoesthesia, irritability, alopecia, dry eye, and hypokalemia were higher in the QNEXA groups than in the placebo group and increased in a dose-related manner. However, few subjects discontinued study drug due to these AEs. In fact, most subjects who experienced a TEAE continued study treatment, and the overall discontinuation rate for any reason was higher in the placebo group than in the QNEXA groups. Overall, the rate of discontinuation from study drug was low and dose-related.

The incidence of SAEs in the 6-month and 1-year cohorts was low and similar across the treatment groups. In particular, the incidence of cardiac SAEs was not increased in the QNEXA groups compared with placebo groups. Only 1 death occurred during the studies, in a placebo-treated subject who died from cardiopulmonary arrest during the first 6 months in study OB-303.

Targeted Medical Events

The incidence of TEAEs in the sleep disorders (mostly insomnia), anxiety, and depression subclasses was higher in some or all QNEXA groups than in the placebo group. Anxiety and depression TEAEs were primarily mild in severity and were considered severe in <1% of subjects in any treatment group. None of the anxiety or depression TEAEs was serious. Importantly, there was no difference between treatment groups in the use of new psychiatric or antidepressant medications during the study.

The incidence of TEAEs categorized as cognitive disorders, including attention and memory impairment, was higher in the Top-dose and Mid-dose groups than in the placebo group, and these TEAEs were primarily mild in severity.

Overall, the incidence of TEAEs in the suicide/self-injury and psychomotor disorders subclasses was low (<1%) across all treatment groups. Furthermore, no TEAEs occurred in the drug abuse and drug withdrawal subclasses in any of the treatment groups.

No clinically important differences among treatment groups in change from baseline safety laboratory parameters were noted. Dose-related decreases in serum bicarbonate, a labeled side effect of topiramate, were observed in the QNEXA groups and were not exacerbated by co-administration of metformin. An increase in mild hypokalemia, another labeled side effect of topiramate, was also observed in the QNEXA groups, primarily in subjects using non-potassium-sparing diuretics. Treatment with QNEXA did not adversely affect liver function, and there was an improvement in AST and ALT compared with placebo. Two cases of elevated liver transaminases with elevated bilirubin were reported; however, in both subjects, these elevations occurred concurrently with SAEs of cholelithiasis, which resolved with treatment.

A total of 34 pregnancies occurred during the QNEXA clinical development program; however, to date, all births have been classified as healthy normal with no malformations or adverse outcomes.

6 CARDIOVASCULAR SAFETY

6.1 Baseline Cardiovascular-Related Conditions

Cardiovascular-related conditions described in this section include dyslipidemia, cardiovascular disease, and hypertension. Definitions for these conditions are provided below.

- Dyslipidemia: Using ≥2 medications for treatment of the condition at baseline or having a baseline triglyceride measurement at or above 200 mg/dL
- Cardiovascular disease: having either (1) a history of CAD, peripheral arterial occlusive disease, or stroke; or (2) diabetes plus ≥1 of the following: current smoker, hypertension, or dyslipidemia
- Hypertension: Using ≥2 medications for treatment of the condition at baseline or having a baseline SBP measurement between 140 and 160 mm Hg (130-160 mm Hg for diabetic subjects) or a baseline DBP measurement between 90 and 100 mm Hg (85-100 mm Hg for diabetic subjects)

Table 29 shows the percentage of subjects with dyslipidemia, cardiovascular disease, and hypertension at baseline in each of the treatment groups.

Table 29. Percentage of Subjects with Cardiovascular-Related Medical Conditions at Baseline (Safety Set, 1-Year Cohort)

Medical Condition	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Dyslipidemia	399 (25.6)	5 (2.1)	180 (36.1)	416 (26.3)
Cardiovascular disease	228 (14.6)	5 (2.1)	74 (14.9)	255 (16.1)
Hypertension	627 (40.2)	33 (13.8)	261 (52.4)	642 (40.6)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

6.2 Cardiac Disorders Adverse Events: Cardiac Arrhythmia and Ischemia Targeted Medical Event Analysis

Cardiovascular adverse reactions historically associated with phentermine include palpitations, tachycardia, and elevation of blood pressure. Association of phentermine and primary pulmonary hypertension and/or regurgitant cardiac valvular disease have not been demonstrated (Adipex-P® package insert 2006).

As shown in **Table 30**, the incidence of TEAEs in the cardiac arrhythmia subclass was higher in the QNEXA Mid- and Top-dose groups than in the QNEXA Low-dose and placebo groups. Most of the TEAEs in this subclass included events associated with changes in heart rate, such as palpitations. Most were mild or moderate in severity for all treatment groups. There was no difference in the incidence of severe cardiac arrhythmia TEAEs among the treatment groups.

Cardiac arrhythmia TEAEs were serious in 4 (0.3%) subjects in the placebo group, 2 (0.4%) in the QNEXA Mid-dose group, and 2 (0.1%) subjects in the QNEXA Top-dose group. Of the 98 subjects on QNEXA treatment who had a cardiac arrhythmia TEAE, 15 (15.3%) subjects discontinued study drug due to the TEAE. Of the 28 placebo-treated subjects who had a cardiac arrhythmia TEAE, 6 (21.4%) discontinued study drug due to the TEAE.

Table 30. Incidence of Treatment-Emergent Adverse Events in the Cardiac Arrhythmia Subclass (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Cardiac arrhythmia subclass	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)
Heart rate increased	1 (0.1)	0	2 (0.4)	12 (0.8)
Tachycardia	1 (0.1)	1 (0.4)	2 (0.4)	11 (0.7)
Syncope	4 (0.3)	0	2 (0.4)	6 (0.4)
Atrial fibrillation	2 (0.1)	0	1 (0.2)	3 (0.2)
Syncope vasovagal	0	0	2 (0.4)	3 (0.2)
Bundle branch block right	2 (0.1)	0	1 (0.2)	1 (0.1)
Arrhythmia	0	0	1 (0.2)	2 (0.1)
Electrocardiogram abnormal	3 (0.2)	0	0	0
Ventricular extrasystoles	1 (0.1)	0	0	2 (0.1)
Atrioventricular block first degree	1 (0.1)	0	0	1 (0.1)
Electrocardiogram QT prolonged	1 (0.1)	0	0	1 (0.1)
ECG repolarization abnormality	0	0	0	2 (0.1)
Heart rate irregular	0	0	0	2 (0.1)
Loss of consciousness	0	0	1 (0.2)	1 (0.1)
Bradycardia	0	0	0	1 (0.1)
Cardiac flutter	0	0	0	1 (0.1)
Cardiorespiratory arrest	1 (0.1)	0	0	0
Extrasystoles	0	0	0	1 (0.1)
Sinus bradycardia	0	1 (0.4)	0	0
Sinus tachycardia	0	0	0	1 (0.1)
Supraventricular extrasystoles	0	0	1 (0.2)	0

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
ECG=electrocardiogram; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

6.2.1 Ischemic Events

The incidence of ischemic events is shown by treatment group in **Table 31**. In the total study population in the 1-year cohort (N=3879), there were 16 SAEs in the Cardiac Disorders SOC, the majority of which were related to cardiac ischemia. The frequency of these ischemic events was similar in placebo and QNEXA treatment groups.

Table 31. Incidence of Ischemic Events (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Cardiac disorders	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Coronary artery disease	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.1)
Angina pectoris	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood CPK increase	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Arteriosclerosis coronary artery	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cardio-respiratory arrest	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Overall, four SAEs were coded as myocardial infarction (MI) in active treatment arms (N=2318), compared with none in the placebo group (N=1561). Additionally, four SAEs of coronary artery disease were reported in placebo subjects, and none were reported in QNEXA-treated subjects: one angina event in the placebo group and one in the QNEXA group; one acute coronary syndrome in the QNEXA group; and, one myocardial ischemia in the placebo group. The only study death – a sudden cardiac death – occurred in a placebo subject. Detailed narratives of cardiac SAEs are provided in **Appendix 6**.

6.3 Vital Signs

Table 32 summarizes the mean changes in blood pressure and heart rate from baseline to endpoint for the 1-year cohort. Mean decreases in SBP and DBP were observed across all treatment groups. Mean decreases in SBP and DBP were larger for the Mid- and Top-dose QNEXA groups compared with the placebo group. Small mean increases in heart rate were observed in the QNEXA treatment groups, and no mean change was observed in the placebo group.

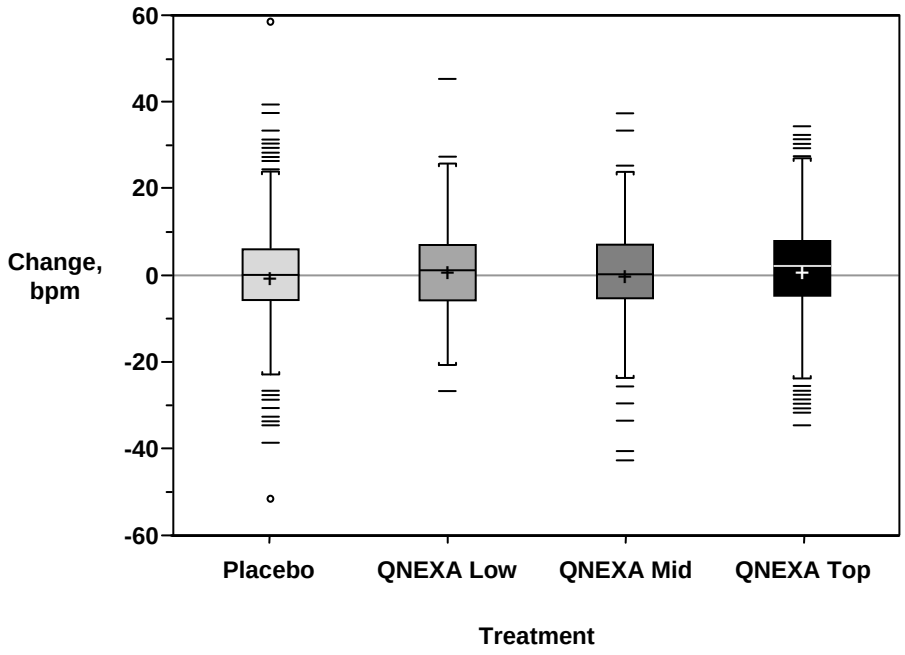
Table 32. Changes in Blood Pressure and Heart Rate From Baseline to Endpoint (Safety Set, 1-Year Cohort)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Systolic blood pressure, mm Hg				
n [1]	1532	234	488	1553
Baseline [2], mean (SD)	126.5 (13.25)	122.5 (11.11)	128.5 (13.63)	125.7 (13.12)
Endpoint [3], mean (SD)	124.3 (13.64)	119.1 (12.24)	123.4 (14.08)	120.5 (13.50)
Mean change (SD)	-2.1 (14.01)	-3.3 (11.95)	-5.2 (14.77)	-5.2 (14.48)
Diastolic blood pressure, mm Hg				
n [1]	1532	234	488	1553
Baseline [2], mean (SD)	79.6 (8.95)	77.8 (7.49)	80.6 (8.71)	79.0 (8.76)
Endpoint [3], mean (SD)	77.7 (9.62)	76.9 (8.24)	77.3 (8.82)	76.1 (8.82)
Mean change (SD)	-1.9 (9.61)	-0.9 (8.29)	-3.3 (9.87)	-2.9 (9.40)
Heart rate, bpm				
n [1]	1532	234	488	1553
Baseline [2], mean (SD)	72.5 (9.58)	72.3 (9.22)	72.2 (10.07)	72.7 (9.87)
Endpoint [3], mean (SD)	72.5 (10.05)	73.6 (9.73)	72.7 (10.34)	74.3 (9.83)
Mean change (SD)	0.0 (10.19)	1.3 (10.32)	0.6 (10.18)	1.6 (10.28)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. n is the number of subjects with baseline and endpoint measurements.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
3. Endpoint is the last available measurement obtained during the double-blind treatment period.
QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Figure 25 presents side-by-side boxplots for the distribution of change in heart rate from baseline to endpoint in each treatment group for the 1-year cohort. The high degree of overlap among all treatment groups suggests no meaningful difference between placebo treatment and QNEXA treatment in the distribution and ranges of observed increases and decreases in heart rate observed at study endpoint.

Figure 25. Side-by-Side Boxplot for Change in Heart Rate From Baseline to Week 56/End of Treatment

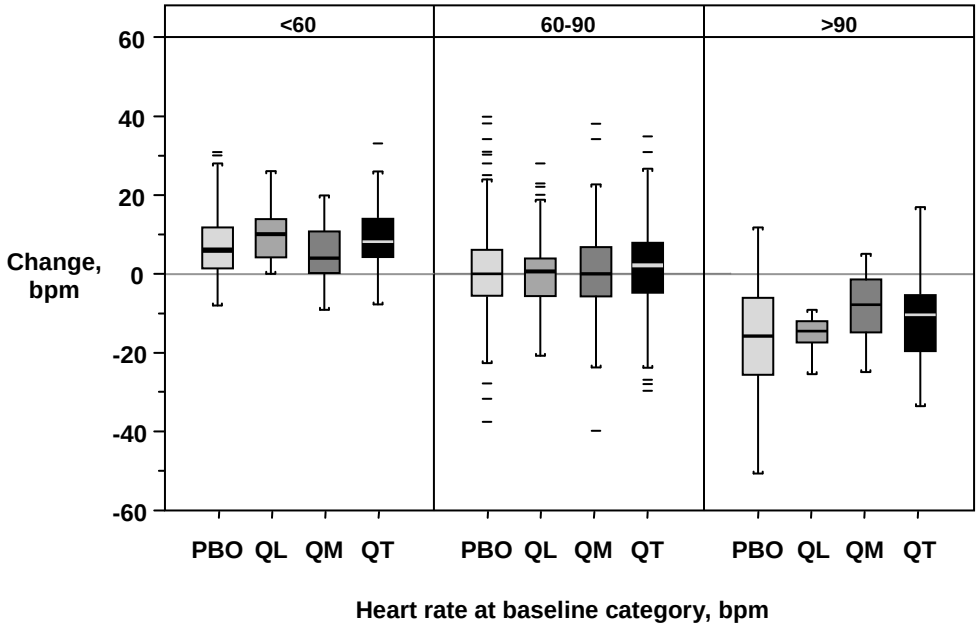


Includes data from studies OB-202/DM-230, OB-302, and OB-303.
Lines on plot show outliers up to a distance of 3 times the interquartile range. Open circles show the outliers beyond 3 times the interquartile range.
QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Figure 26 illustrates change in heart rate with respect to baseline heart rate. These results demonstrate that across all treatment groups, subjects with heart rates between 60 and 90 bpm at baseline showed little change from baseline. In all treatment groups, subjects with heart rates <60 bpm at baseline showed heart rate increases, which were not markedly different among treatment

groups. Subjects with heart rates >90 bpm at baseline demonstrated heart rate decreases with treatment; the greatest decreases were observed for the placebo and QNEXA Low-dose groups.

Figure 26. Heart Rate Change by Baseline Heart Rate



PBO=placebo; QL=QNEXA Low, 3.75/23 mg; QM=QNEXA Mid, 7.5/46 mg; QT=QNEXA Top, 15/92 mg.

Table 33 summarizes concurrent systolic blood pressure changes in heart rate outliers.

Table 33. Systolic Blood Pressure Changes in Heart Rate Outliers (Safety Set, 1-Year Cohort)

Outlier Category	Placebo (N=1561)	QNEXA Low (N=240)	QNEXA Mid (N=498)	QNEXA Top (N=1580)
>10 bpm				
n	657	120	251	887
Mean concurrent change (mmHg)	-1.9	-1.8	-6.3	-4.6
>20 bpm				
n	186	36	67	309
Mean concurrent change (mmHg)	-1.6	-0.1	-5.2	-4.4

QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Results for changes in systolic blood pressure and heart rate for the 6-month cohort were similar to those for the 1-year cohort.

Table 34 provides a summary of the change in the rate-pressure product (RPP) from baseline to Week 56. The RPP is defined as the product of heart rate (bpm) and SBP (mm Hg) divided by 1000, correlating with myocardial oxygen demand (White 1999). The mean change in RPP was -0.22 for the placebo group, -0.30 for the QNEXA Low-dose group, -0.39 for the QNEXA Mid-dose group, and -0.27 for the QNEXA Top-dose group. All treatment groups demonstrated statistically significant reductions in RPP from baseline to Week 56 ($p<0.05$). Treatment comparisons between all QNEXA groups and placebo group for change in RPP from baseline to Week 56 were not statistically significant.

Table 34. Change in Rate-Pressure Product From Baseline to Week 56 and Treatment Comparisons (Safety Set, 1-Year Cohort – Phase 3 Studies)

Treatment	n [1]	Baseline [2] Mean (SD)	Week 56 Mean (SD)	Change [3]		
				Mean (SD)	LS Mean (SE)	p-value
Placebo	888	9.17 (1.570)	8.98 (1.635)	-0.19 (1.734)	-0.22 (0.053)	<0.0001
QNEXA Low	147	9.16 (1.523)	8.84 (1.495)	-0.32 (1.560)	-0.30 (0.125)	0.0161
QNEXA Mid	374	9.25 (1.591)	8.87 (1.607)	-0.39 (1.813)	-0.39 (0.084)	<0.0001
QNEXA Top	1073	9.18 (1.566)	8.93 (1.518)	-0.25 (1.681)	-0.27 (0.048)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [3]		
	LS Mean (SE)	95% CI	p-value
QNEXA Top (Tmt 1) vs Placebo (Tmt 2)	-0.05 (0.065)	(-0.18, 0.08)	0.4608
QNEXA Mid (Tmt 1) vs Placebo (Tmt 2)	-0.17 (0.091)	(-0.34, 0.01)	0.0704
QNEXA Low (Tmt 1) vs Placebo (Tmt 2)	-0.08 (0.137)	(-0.35, 0.19)	0.5595

Data from studies OB-302 and OB-303 are included.
1. n is the number of subjects with values at both time points.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
3. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, study, and sex as fixed effects and baseline as a covariate.
CI=confidence interval; LS=least squares; QNEXA=fixed-dose combination of phentermine and topiramate; SD=standard deviation; SE=standard error; Tmt=treatment.

6.4 Corrected QT Interval Data (Phase 3 Program)

The incidence of QTcB and QTcF elevations >500 msec at the final visit, during the titration phase, and during the maintenance phase was low (<1%) and similar across all treatment groups. No major differences were observed among the placebo and QNEXA treatment groups in the incidence of QTcB or QTcF changes from baseline >60 msec at the final visit, during the titration phase, or during the maintenance phase.

6.5 Thorough QT/QTc Study Results

See **Section 3.4.4**.

6.6 Echocardiogram Results

OB-201 was a double-blind, single-center, proof-of-concept study, which contributed data from 50 subjects treated with the combination of phentermine and topiramate, 50 subjects treated with

phentermine alone, 50 subjects treated with topiramate alone, and 50 subjects who received placebo. An echocardiogram was performed at baseline and at the end of the study to assess the presence of any valvular heart abnormalities, using FDA criteria (Centers for Disease Control and Prevention 1997) for cardiac valvulopathy of aortic regurgitation of mild or greater severity and/or mitral regurgitation of moderate or greater severity. All echocardiograms were assessed by a cardiologist blinded to treatment assignment. None of the therapies studied (phentermine/topiramate combination therapy, phentermine monotherapy, or topiramate monotherapy), was associated with clinically significant changes in heart valve morphology after 24 weeks of treatment. There were no cases of aortic or mitral regurgitation meeting the FDA threshold definition for cardiac valvulopathy.

6.7 Summary of Cardiovascular Safety

Overall, the rate of major cardiovascular events in the 1-year cohort was low (<1%), but there appears to be no increased risk of major cardiovascular SAEs in the QNEXA treatment groups compared with the placebo group. Consistent reductions in both SBP and DBP were observed across all studies. Small dose-related increases in heart rate were associated with lower starting baseline values, and these changes in heart rate were associated with concurrent reductions in blood pressure. The rate-pressure product was reduced during treatment, indicating no increase in myocardial oxygen demand.

The results from a thorough QT study (study OB-118) demonstrated that QNEXA has no effect on cardiac repolarization of clinical or regulatory concern., and the echocardiographic data from study OB-201 showed that QNEXA treatment does not result in changes in heart valve morphology.

6.7.1 Discussion of Ischemic Events

The pivotal trials of the QNEXA Phase 3 program were designed to study two different populations: (1) subjects with Class II or higher obesity (BMI ≥35 kg/m^2) without significant co-morbidities (study OB-302), and (2) subjects who were overweight or obese (BMI ≥27 kg/m^2) with significant co-morbidities, such as hypertension, dyslipidemia, and diabetes (study OB-

303). The objective was to assess both efficacy and safety in these two, broadly defined populations that would represent the most likely initial candidates for weight loss therapy.

While 52.5% of the subjects enrolled into OB-303 had a history of hypertension, 36.1% dyslipidemia, 66.7% impaired fasting glucose, and 15.8% type 2 diabetes mellitus, the prevalence of more advanced cardiovascular disease was lower. Six percent of the OB-303 population reported a history of cardiac disorders of any kind, 3.9% a cardiac murmur, 1.5% a previous myocardial infarction, 1.1% coronary artery disease, 0.6% atrial fibrillation, and 0.1% congestive heart failure. In addition, the mean baseline Framingham 10-year risk for the 1-year cohort was <5; values <10 are classified as low risk.

A total of 16 SAEs in the Cardiac Disorders SOC were reported in a total of 3879 subjects in the 1-year cohort. The majority of these events were related to cardiac ischemia, and the frequency of ischemic events was similar between the placebo and QNEXA treatment groups.

Obesity is a causative factor for major adverse cardiac events, however in most cases, obesity precedes these events by many years. Therefore, the ideal time to treat for *prevention* of major cardiac events in obese patients is to treat *before* the cumulative insult of obesity has occurred. The study population in these trials was significantly younger than populations recruited for most outcome-type trials, and the relatively young age of subjects contributed to the relatively low rate (<1%) of major cardiovascular events observed in these trials.

Serious cardiac adverse events were examined in all subjects included in the Integrated Safety Analysis of the NDA. Overall, there were eight cardiac SAEs in the QNEXA groups (N=2559) and nine in the placebo group (N=1719). The relative risk was 0.60 (95% CI: 0.23-1.54), QNEXA vs. placebo. There were four SAEs coded as MIs in active treatment arms compared with none in the placebo group. There were additional ischemic events, such as coronary artery disease, angina pectoris (resulting in emergency revascularization), acute coronary syndrome, and myocardial ischemia, which occurred more frequently in the placebo group. Review of the narratives for these events reveals that four placebo subjects required emergent coronary revascularization, vs one on active treatment. The only study death – a sudden cardiac death – occurred in a placebo subject. Another placebo subject required two hospital admissions for

acute exacerbation of congestive heart failure and also experienced a cardiac arrest, from which he was successfully resuscitated.

Overall, the frequency of serious cardiac adverse events was low. On the basis of the sample size, study duration, and the rate of all serious cardiac events , there is no apparent difference in serious cardiovascular risk with QNEXA versus placebo treatment.

7 PSYCHIATRIC AND COGNITIVE SAFETY

7.1 Psychiatric Assessment

7.1.1 Psychiatric History of Phase 3 Population

The Phase 3 population did not exclude subjects with a history of suicidal ideation, presence of mild depression, depression managed by antidepressant medications (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]), or one episode of major depression.

Approximately 26% to 30% of subjects had a history of psychiatric disorders, 18% to 20% had a history of depression, and 14% were taking concomitant antidepressant medications.

7.1.2 Adverse Events

Table 35 presents the incidence of TEAEs categorized as TMEs in the Psychiatric Disorders class for the Safety set, and **Table 36** summarizes discontinuations associated with psychiatric AEs.

As shown in **Table 35**, the incidence of TEAEs in the sleep disorders and depression (SMQ) subclasses was higher in the QNEXA Top-dose group than in the other treatment groups, and the incidence of TEAEs in the anxiety subclass was higher in all QNEXA groups compared with the placebo group. Two events were reported in the suicide/self-injury subclass: one in the placebo group and one in the QNEXA Low-dose group; each of these events were suicidal ideation without intent.

Table 35. Incidence of Treatment-Emergent Adverse Events Categorized as Targeted Medical Events in the Psychiatric Disorders Class (Safety Set, 1-Year Cohort)

TME Class TME Subclass	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Psychiatric disorders class	161 (10.3)	38 (15.8)	72 (14.5)	325 (20.6)
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Depression (SMQ) subclass [1]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0	0

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
QNEXA=fixed-dose combination of phentermine and topiramate; SMQ=standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME=targeted medical event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

Table 36. Number and Percentage of Subjects Discontinued Due to TEAEs in Psychiatric TME (Safety Set, 1-Year Cohort)

Events	Placebo (N=1561)	QNEXA Low (N=240)	QNEXA Mid (N=498)	QNEXA Top (N=1580)
Sleep disorder subclass	**7 (0.4)**	**0 (0.0)**	**2 (0.4)**	**26 (1.6)**
Insomnia	6 (0.4)	0 (0.0)	2 (0.4)	25 (1.6)
Depression (SMQ) subclass	**4 (0.3)**	**2 (0.8)**	**5 (1.0)**	**28 (1.8)**
Depression	3 (0.2)	0 (0.0)	4 (0.8)	21 (1.3)
Depressed Mood	1 (0.1)	1 (0.4)	1 (0.2)	1 (0.1)
Mood Altered	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Anxiety subclass	**6 (0.4)**	**2 (0.8)**	**5 (1.0)**	**33 (2.1)**
Irritability	1 (0.1)	2 (0.8)	4 (0.8)	18 (1.1)*
Anxiety	4 (0.3)	0 (0.0)	1 (0.2)	17 (1.1)*
Suicide/self-injury subclass	**1 (0.1)**	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**
Suicide Ideation	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
*Irritability was under the System Organ Class of General Disorders and Administration Site Conditions, while anxiety was under the System Organ Class of Psychiatric Disorders. Although a subject may have had two or more TEAEs, the subject is counted only once within a subclass.
QNEXA=fixed-dose combination of phentermine and topiramate; SMQ=standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TEAEs=treatment-emergent adverse events.
QNEXA Low, 3.75/23 mg; QNEXA Mid or recommended dose, 7.5/46 mg; QNEXA Top, 15/92 mg.

7.1.2.1 Depression (SMQ) Events

Overall, the discontinuation rate due to AEs in the depression (SMQ) subclass was 0.3% (4/1561) for the placebo group and 1.5% (35/2318) for the QNEXA treatment groups, indicating that most subjects with depression-related AEs continued on study **(see Tables 35 and 36 above)**. For presentation of severity of depression group events, please see **Section 5.4.4.1, Table 20.**

Table 37 summarizes the frequency of adverse events by preferred term in the depression (SMQ) subclass for the 1-year cohort. Events of depression were most commonly reported in this subclass, and by a higher percentage of subjects in the QNEXA Top-dose group than in the other treatment groups. However, the percentage of subjects with new antidepressant use during study was similar across all treatment groups (placebo, 3.7%; QNEXA Low-dose, 4.6%; Mid-dose, 2.4%; and Top-dose, 3.0%).

Table 37. Frequency of Adverse Events in the Depression (SMQ) Subclass (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Depression (SMQ) subclass [1]	**53 (3.4)**	**12 (5.0)**	**19 (3.8)**	**121 (7.7)**
Depression	35 (2.2)	8 (3.3)	14 (2.8)	68 (4.3)
Depressed mood	9 (0.6)	2 (0.8)	2 (0.4)	9 (0.6)
Mood altered	5 (0.3)	1 (0.4)	1 (0.2)	15 (0.9)
Mood swings	4 (0.3)	0 (0.0)	0 (0.0)	13 (0.8)
Affect lability	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)
Crying	1 (0.1)	0 (0.0)	1 (0.2)	4 (0.3)
Apathy	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)
Dysphoria	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Tearfulness	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Anhedonia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Decreased interest	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Dysthymic disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Feeling of despair	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Listless	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Self-esteem decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
1. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
QNEXA=fixed-dose combination of phentermine and topiramate; SMQ=standardized Medical Dictionary for Regulatory Activities (MedDRA) query.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

7.1.2.2 Anxiety-Related Events

Overall, events in the anxiety subclass (event terms: anxiety, irritability, agitation) occurred in 2.6% (41/1561) of placebo-treated subjects and 6.9% (160/2318) of QNEXA-treated subjects. These events were mostly mild or moderate in intensity, with severe events occurring in 0.2% (3/1561) of placebo subjects and 0.6% (13/2318) of subjects treated with QNEXA. There were no serious anxiety-related events in any treatment group. For presentation of severity of Anxiety Group events, please see **Section 5.4.4.1, Table 20.**

Overall, the discontinuation rate due to AEs in the anxiety subclass was 0.4% (6/1561) for the placebo group and 1.7% (40/2318) for the QNEXA treatment groups, indicating that most subjects with anxiety-related AEs continued on study (see **Tables 35 and 36** above).

7.1.3 PHQ-9 Results

To assess and monitor the risk of depression, the PHQ-9 questionnaire was administered to each subject at each study visit. Shifts in PHQ-9 scores from baseline to highest (worst) score during the double-blind treatment period were summarized by treatment group for the 6-month and 1-year cohorts. Baseline and post-baseline scores for depression severity were grouped according to the scale provided with the PHQ-9, where 0–4=no depression, 5–9=mild depression, 10–14=moderate depression, 15–19=moderately severe depression, and 20–27=severe depression.

Responses to PHQ-9 question 9 (“thoughts that you would be better off dead, or of hurting yourself in some way”) were summarized by treatment group, combined QNEXA group, and overall at each visit.

The PHQ-9 instrument is a nine-item patient-completed questionnaire, with a score of 0 to 3 assigned to each item. From the PHQ-9 assessments in the individual studies, all of the treatment groups had mean decreases in the PHQ-9 total score. No clinically important differences were noted among the treatment groups in mean changes in the PHQ-9 score. The summary of worsening shifts in PHQ-9 depression severity by treatment group likewise did not reveal any treatment-related patterns.

7.1.3.1 Change in PHQ-9 Depression Severity From Baseline to Highest Score

Table 38 presents the number and percentage of subjects in the 1-year cohort with worsened or improved PHQ-9 depression severity from baseline to the highest score.

Table 38. Number and Percentage of Subjects With Worsened or Improved PHQ-9 Depression Severity From Baseline (Safety Set, 1-Year Cohort)

Depression Shift from Baseline Categories	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Worsened PHQ-9 depression,	60 (3.8)	6 (2.5)	10 (2.0)	60 (3.9)
Improved PHQ-9 depression	157 (10.1)	25 (10.4)	60 (12.0)	172 (10.9)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
PHQ-9=9-item Patient Health Questionnaire; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

7.1.3.2 Positive Response to PHQ-9 Question 9

Few subjects in the 1-year cohort had a positive response to PHQ-9 question 9 ("thoughts that you would be better off dead, or of hurting yourself in some way") on several days, more than half the days, or nearly every day at a time point after randomization. The percentage of subjects with a positive response at any time post-randomization to PHQ-9 question 9 after randomization was similar across the treatment groups (placebo, 27 [1.7%]; QNEXA Low dose, 4 [1.7%]; QNEXA Mid dose, 6 [1.2%]; and QNEXA Top dose, 24 [1.5%]).

Additionally, the percentage of subjects with a positive response to PHQ-9 question 9 at ≥2 consecutive visits after randomization or with a positive response at the final visit was low and similar across the treatment groups (placebo, 6 [0.4%]; QNEXA Low dose, 1 [0.4%]; QNEXA Mid dose, 3 [0.6%]; and QNEXA Top dose, 6 [0.4%]).

7.1.3.3 Elevated PHQ-9 Scores During Double-Blind Treatment Period

Table 39 summarizes the number and percentage of subjects by three categories of elevated PHQ-9 total scores corresponding to moderate or worse depression during the double-blind treatment period for the 1-year cohort. A slight numerical increase was seen in the QNEXA Top-dose group relative to other treatment groups in the incidence of post-randomization PHQ-9 scores ≥15.

Table 39. Summary of Elevated PHQ-9 Scores During the Double-Blind Treatment Period (Safety Set, 1-Year Cohort)

Time Point PHQ-9 Total Score	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Any time post-randomization				
≥10	103 (6.6)	11 (4.6)	23 (4.6)	104 (6.6)
≥15	13 (0.8)	3 (1.3)	2 (0.4)	23 (1.5)
≥20	3 (0.2)	0	1 (0.2)	7 (0.4)
At final visit				
≥10	25 (1.6)	5 (2.1)	7 (1.4)	21 (1.3)
≥15	3 (0.2)	2 (0.8)	1 (0.2)	4 (0.3)
≥20	0	0	1 (0.2)	1 (0.1)
During titration phase				
≥10	36 (2.3)	1 (0.4)	11 (2.2)	48 (3.0)
≥15	4 (0.3)	0	1 (0.2)	11 (0.7)
≥20	0	0	1 (0.2)	4 (0.3)
During maintenance phase				
≥10	75 (4.8)	11 (4.6)	13 (2.6)	69 (4.4)
≥15	9 (0.6)	3 (1.3)	1 (0.2)	14 (0.9)
≥20	3 (0.2)	0	0	3 (0.2)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
All measurements taken during the double-blind treatment period are considered.
The titration phase is the period of time from the first dose of double-blind study drug up to and including the Week 4 visit date. For subjects continuing beyond Week 4, the Week 4 visit date is the cutoff. The maintenance phase is defined as the period of time from the Week 4 visit date to the date of completion or early termination from the study.
PHQ-9=9-item Patient Health Questionnaire; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

7.1.4 Columbia-Suicide Severity Rating Scale Results

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an 11-item clinician-administered assessment of both suicidal behavior (5 items) and suicidal ideation (6 items) provided at every visit in the Phase 3 development program for QNEXA. Each of the items comprising this scale corresponds to a specific level or severity of ideation or behavior, and is answered on a yes/no basis.

As part of the original NDA, for each item of the C-SSRS, the number of *yes* responses at any time during the double-blind treatment period was summarized by treatment group, for the combined QNEXA group, and overall for the 6-month and 1-year cohorts. A composite measure that included the following items was also summarized for the double-blind treatment period:

active suicidal ideation with some intent to act without specific plan; active suicidal ideation with specific plan and intent; suicidal behavior, which includes actual attempt; engagement in nonsuicidal, self-injurious behavior; interrupted attempt; aborted attempt; and, preparatory acts or behavior.

In the QNEXA clinical program, 3 subjects had a positive response to the C-SSRS composite measure at a time point after randomization: 2 (0.1%) subjects in the placebo group and 1 (0.1%) subject in the QNEXA Top-dose group. None of the responses to the nonspecific "suicidal behavior" question were accompanied by positive responses to specific behaviors. By excluding subjects whose only positive response was to the nonspecific "suicidal behavior" question, only two subjects had a positive response to the C-SSRS composite measure subsequent to initiation of study treatment. Only two subjects, both of whom were in the 6-month cohort, reported any suicidal behavior: Subject118-030 (OB-301; placebo) and Subject 112-016 (OB-301; single-agent TPM 92 mg). No subjects on QNEXA treatment reported any suicidal behavior in either the 6-month or 1-year cohort.

Two of the positive responses to the C-SSRS composite measure (one subject in the placebo group and one subject in the QNEXA Top-dose group) were based on *yes* responses to the nonspecific question addressing the presence of "any suicidal behavior." None of the responses to the nonspecific "suicidal behavior" question were accompanied by positive responses to specific behaviors.

Table 40 summarizes the analysis of the C-SSRS for the 1-year cohort as described in the Data Analysis Plan by the Center for Suicidality Risk Assessment. This method of analysis is recommended by the authors of the C-SSRS and has been provided to the FDA as the approach that should be used to analyze outcomes on this instrument.

No reports of suicidal behavior were observed in any treatment group. The percentage of subjects with reports of suicidal ideation was low (<1%) and similar across all treatment groups. All reports of suicidality (suicidal behavior or suicidal ideation) were reports of suicidal ideation; thus the percentage of subjects in this category is the same as those for suicidal ideation.

Table 40. Summary of C-SSRS as Recommended by the Center for Suicidality Risk Assessment (Safety Set, 1-Year Cohort)

Category Subcategory	Placebo (N=1506) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1505) n (%)	p-value [1]
Suicidal behavior	0	0	0	0	n/a
Actual attempt	0	0	0	0	
Aborted attempt	0	0	0	0	
Interrupted attempt	0	0	0	0	
Preparatory acts or behaviors	0	0	0	0	
Suicidal ideation	11 (0.7)	1 (0.4)	3 (0.6)	14 (0.9)	0.8901
Wish to be dead	9 (0.6)	1 (0.4)	3 (0.6)	13 (0.9)	
Nonspecific active suicidal thoughts	5 (0.3)	1 (0.4)	1 (0.2)	6 (0.4)	
Active suicidal ideation with any methods without intent to act	2 (0.1)	0	0	1 (0.1)	
Active suicidal ideation with some intent to act without specific plan	0	0	0	0	
Active suicidal ideation with specific plan and intent	0	0	0	0	
Suicidality (suicidal behavior or suicidal ideation)	11 (0.7)	1 (0.4)	3 (0.6)	14 (0.9)	0.8901

Data from studies OB-302 and OB-303 are included.
All measurements taken during the double-blind treatment period are considered.
1. p-value is obtained from Fisher's exact test for testing that the response to each C-SSRS category is independent of treatment group.
C-SSRS=Columbia Suicide Severity Rating Scale; n/a=not applicable, no p-value can be calculated when no positive responses within a given category are observed; QNEXA=fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

In separate "treatment-emergent" analyses, there were no significant differences between treatment groups in incidence of emergent or worsening ideation.

No reports of suicidal behavior were observed in any treatment group, and no significant differences were observed among treatment groups for the comparisons of positive responses in any of the C-SSRS categories.

7.2 Cognitive Assessment

7.2.1 Adverse Events

Table 41 presents the incidence of TEAEs categorized as TMEs in the Cognitive Disorders class. In this class, the incidence of TEAEs in the attention and memory impairment subclasses was higher in the QNEXA Mid- and Top-dose groups than in the QNEXA Low-dose and placebo groups. The incidence of TEAEs in the language and other cognitive disorders subclasses was low overall, but higher in the QNEXA Top-dose group compared with the other treatment groups. For presentation of severity of Cognitive Class events, please see **Section 5.4.4.1, Table 20**. There were no AEs that led to discontinuation in ≥1% of subjects.

Table 41. Proportion of Subjects With Treatment-Emergent Adverse Events Categorized as Targeted Medical Events by Class and Subclass (Safety Set, 1-Year Cohort)

TME Class TME Subclass	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Cognitive disorders class				
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Language subclass	1 (0.1)	0	3 (0.6)	19 (1.2)
Other cognitive disorders NOS subclass	5 (0.3)	2 (0.8)	5 (1.0)	28 (1.8)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
NOS=not otherwise specified; QNEXA=fixed-dose combination of phentermine and topiramate; TME=targeted medical event.
QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.

7.2.1.1 Attention Events

Overall, events in the attention subclass (event terms: disturbance in attention, depressed level of consciousness) occurred in 0.6% (10/1561) of placebo-treated subjects and 2.9% (67/2318) of QNEXA-treated subjects. These events were mostly mild or moderate in intensity, with severe events occurring in 0.1% (1/1561) of placebo subjects and 0.1% (1/2318) of subjects treated with QNEXA. There were no serious attention-related events in any treatment group.

Overall, the discontinuation rate due to AEs in the Attention subclass was 0.2% (3/1561) for the placebo group and 0.6% (15/2318) for the QNEXA treatment groups, indicating that most subjects with attention-related AEs continued on study.

7.2.1.2 Memory Impairment Events

Overall, events in the memory impairment subclass (event terms: memory impairment, amnesia) occurred in 0.6% (10/1561) of placebo-treated subjects and 2.2% (51/2318) of QNEXA-treated subjects. These events were mostly mild or moderate in intensity, with severe events occurring in no placebo-treated subjects and 0.1% (1/2318) of subjects treated with QNEXA. There were no serious memory impairment events in any treatment group.

Overall, the discontinuation rate due to AEs in the memory impairment subclass was 0.1% (2/1561) for the placebo group and 0.5% (12/2318) for the QNEXA treatment groups, indicating that most subjects with memory impairment AEs continued on study.

7.2.2 Repeatable Battery for Assessment of Neuropsychological Status Results

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was used to assess cognitive functioning in the individual 6-month studies OB-202 and OB-301. Cognitive Drug Research conducted an independent analysis of the RBANS data from both studies. In study OB-202, the treatment comparisons of the RBANS scores at Week 28 showed a statistically significant decrement in the RBANS attention score and the total scale score for the combination therapy group (phentermine 15 mg/topiramate 100 mg) compared with the placebo

group. The results of RBANS in study OB-202 were consistent with the AE profile observed in the study.

In study OB-301, the only difference in cognitive testing observed between QNEXA and placebo was a decrease in the RBANS attention score. There were no clinically meaningful treatment differences in mean change in any other domains of the RBANS, such as immediate memory, visuospatial/constructional, language, and delayed memory scores. The results of RBANS in study OB-301 were consistent with the AE profile observed in the study.

7.3 Psychomotor Assessment

Results from study OB-205, a randomized, double-blind crossover design study that evaluated 45 subjects, showed that psychomotor performance on the Cogscreen® Pathfinder Number Test was significantly deteriorated by alcohol (compared with placebo) at the 0.10 and 0.07 breath alcohol concentration (BrAC) levels. In contrast, when subjects were titrated to QNEXA Mid dose and placebo over a 2-week period, there was no significant difference between QNEXA Mid dose and placebo at either 2 hours or 6 hours post-dosing. Similarly, when subjects continued titration up to the QNEXA Top dose and placebo over Weeks 3 and 4, there was no significant difference between QNEXA Top dose and placebo at either 2 hours and 6 hours post-dosing on this measure of psychomotor speed and coordination.

The secondary measures of psychomotor performance showed significant differences between alcohol and placebo on 8 of 10 measures at the 0.10 BrAC level and on 7 of 10 measures at the 0.07 BrAC level. In contrast, subjects treated with QNEXA performed as well as placebo on 8 of 10 measures. One exception was that on the Pathfinder test at Week 4, subjects on QNEXA were 0.04 seconds slower compared to when they were on placebo, but on the same task they were significantly more coordinated on QNEXA. The slowing in Pathfinder speed was less than that observed at the 0.07 BrAC level. The other exception was that subjects treated with QNEXA had more tracking failures (i.e., boundary hits) at 2 hours post-dose at Week 2, but at the same time point they had significantly lower tracking error scores than during placebo treatment.

7.4 Summary of Psychiatric and Cognitive Safety

QNEXA, primarily at the Top dose, was associated with an increased incidence of psychiatric AEs and study discontinuations due to these AEs. Approximately 90% of QNEXA-associated psychiatric AEs were mild or moderate in severity. There was no difference in the use of new psychiatric or antidepressant medications across treatment groups during the study. Treatment with QNEXA did not increase the risk of suicidality in a population with a significant history of depression (~20%). Furthermore, there were no serious depression or anxiety, no suicide, suicidal attempts, or active suicidal ideation were reported.

The overall incidence of psychiatric AEs was higher in subjects with a history of depression than in subjects without a history of depression; however, the distribution of events across treatment groups relative to placebo did not appear to be meaningfully altered.

The overall incidence of cognitive-related AEs was low and dose related. Most cognitive-related AEs were mild or moderate in severity. Most common cognitive-related AEs included attention and memory. Discontinuations due to cognitive-related AEs were infrequent, but occurred more frequently in QNEXA-treated subjects than subjects who received placebo. Cognitive-related events resolved upon study drug discontinuation. There were no serious adverse changes in cognitive function.

8 BENEFITS AND RISKS

The clinical program for QNEXA was conducted in accordance with the FDA's February 2007 Guidance for Industry: Developing Products for Weight Management (Food and Drug Administration 2007; **Appendix 2**). In the guidance document, the FDA provides standards for development of new drugs for the treatment of obesity. On the basis of accumulated evidence of the long-term health consequences of obesity and its co-morbidities, the FDA has supported the development of safe pharmacologic therapies to be used long term for weight management in individuals at particular risk. Individuals with BMI ≥30 or ≥27 kg/m^2 who also have weight-related co-morbidities are considered appropriate populations for receiving treatment with weight-management drugs and were included across the QNEXA development program.

The Phase 3 studies of QNEXA included three dose levels: Low dose, PHEN/TPM 3.75/23 mg; Mid dose, PHEN/TPM 7.5/46 mg; and Top dose, PHEN/TPM 15/92 mg. QNEXA Mid dose is the recommended treatment dose. QNEXA Top dose is intended for subjects on QNEXA Mid dose who have not achieved adequate weight loss or improvements in weight-related co-morbidities. QNEXA Low dose is the recommended starting dose and may be considered for chronic use as a treatment dose in some subjects based on their individual treatment goals and/or their ability to tolerate the Mid dose.

The doses of phentermine (15 mg) and topiramate (92 mg) that comprise QNEXA Top dose are substantially lower than the maximum approved doses of either monotherapy for their respective indications.

The design and analyses of the QNEXA clinical program focused on subjects at high risk for obesity-related morbidity and mortality, thus representing a population with high medical need. The largest pivotal studies, study OB-302 and study OB-303, were specifically designed to assess the effect of QNEXA treatment on subjects who are morbidly obese and subjects with weight-related co-morbidities, respectively. Study OB-202 evaluated QNEXA treatment in obese subjects with diabetes across the spectrum of disease severity. Approximately 60% of the subjects in study OB-202 had diabetes for 5 or more years and approximately 60% required two or more antidiabetic medications. Study OB-201 and study OB-301 evaluated the effects of QNEXA in relatively healthy obese subjects.

The efficacy and safety results of the clinical studies presented herein support the marketing application of QNEXA as a weight-loss agent.

The effects of QNEXA on weight loss were substantial and readily met the FDA efficacy benchmarks for clinically significant weight loss. Additionally, significant drug-related improvements in co-morbidities were observed with QNEXA treatment.

There was no evidence of any new or unexpected safety issues with QNEXA relative to phentermine or topiramate monotherapy. Based on thorough evaluations of clinical status, laboratory assessments, review and analysis of adverse events, use of questionnaire instruments

to assess cognitive function as well as mood and suicidality, and study of potential psychomotor effects of QNEXA, there were no signals of significant adverse effects in any of these areas.

8.1 Benefits of Treatment

8.1.1 Treatment Effects on Weight-Related Parameters

Placebo-subtracted weight-loss results across each of the Phase 3 studies were both statistically significant and compared favorably to the labeled effects of currently approved weight-loss therapies. According to the Meridia® product label, the recommended (10 mg) and maximum (15 mg) doses are associated with placebo-subtracted weight loss of 2.9% to 3.5% and 4.6% to 4.8%, respectively, based on a baseline body weight of approximately 100 kg (Meridia® package insert 2009). According to the Xenical® product label, the recommended dose is associated with a placebo-subtracted weight loss of approximately 3.5% after 1 year of treatment (Xenical® package insert 2009). Recognizing that such cross-study comparisons permit no definitive conclusions of differences or similarities between different drugs, the recommended doses of both Meridia and Xenical nonetheless appear to produce the same weight loss as QNEXA Low dose. By contrast, treatment with higher doses of QNEXA resulted in placebo-subtracted weight loss of up to 9.4%. Patients who tolerated and used study drug for the intended treatment course lost nearly 14% of their baseline body weight.

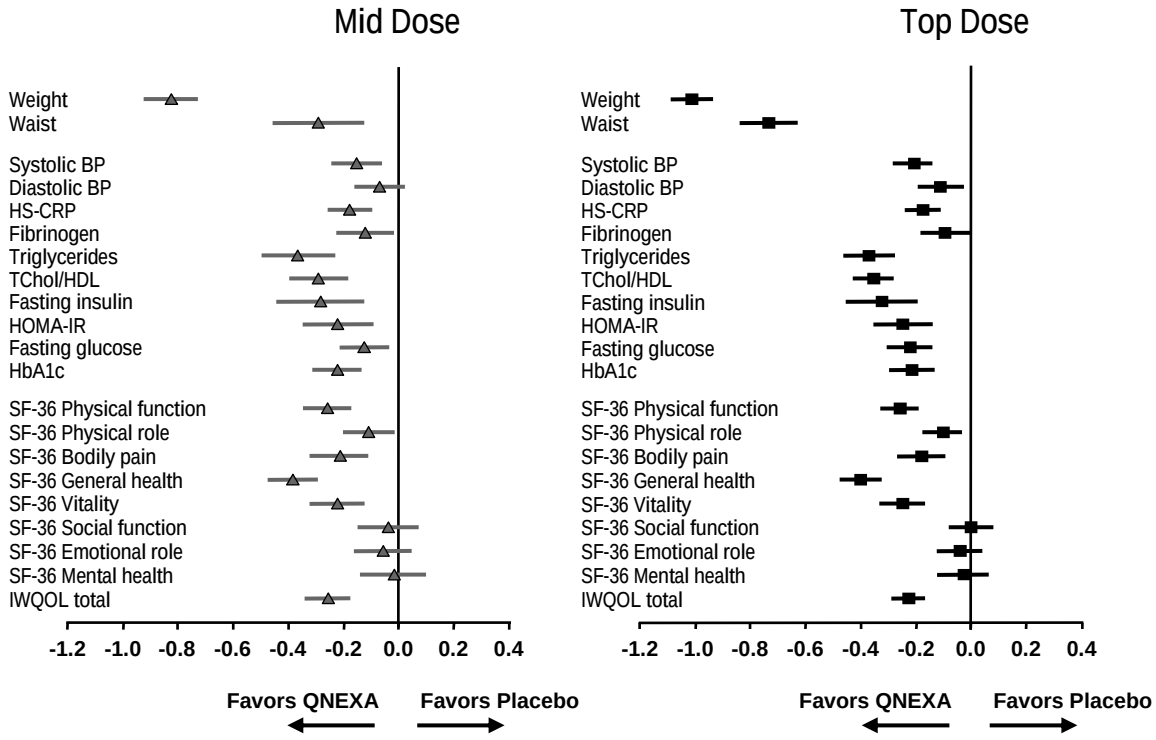
With respect to the categorical assessment of weight loss, significantly greater proportions of subjects treated with QNEXA Low, Mid, and Top dose achieved at least 5%, 10%, and 15% weight loss compared with placebo. From the ITT analysis with LOCF, the response rates for at least 5% weight loss from baseline in study OB-302 and study OB-303 were 67% and 70%, respectively, with QNEXA Top-dose treatment, and 17% and 21%, respectively, with placebo treatment. From the modified ITT analysis without LOCF, the response rates for at least 5% weight loss from baseline in study OB-302 and study OB-303 were 84% and 85%, respectively, with QNEXA Top-dose treatment, and 26% and 26%, respectively, with placebo treatment. At least 10% weight loss was achieved by approximately two-thirds of subjects who completed 56 weeks of treatment with QNEXA Top dose (68% in study OB-302 and 64% in study OB-303). At least 15% weight loss was also achieved by a substantial proportion of subjects who

completed 56 weeks of treatment with QNEXA Top dose (48% in study OB-302 and 39% in study OB-303). Integrated analyses demonstrated that the response rates for 5%, 10%, and 15% weight loss from baseline were statistically significant and consistent with the results of the individual studies.

The integrated 1-year cohort analyses also demonstrated that treatment with QNEXA resulted in clinically and statistically significant weight loss in all subgroups examined, defined by sex, age, race, and baseline BMI. Study-specific and PK/PD analyses indicate that the effect of QNEXA Top-dose treatment on weight loss is generally greater with increasing baseline BMI and suggest that weight loss continues for a longer period of time with increasing BMI. In study OB-302, weight loss was progressive through Week 56 in the QNEXA Top-dose group, which included subjects with a higher mean baseline BMI (42.1 kg/m^2) than study OB-303 (36.6 kg/m^2). In study OB-303, weight loss in the QNEXA Top-dose group remained stable beyond Week 40.

As shown in **Figure 27**, a number of secondary efficacy parameters were assessed to investigate whether the weight loss associated with QNEXA therapy was accompanied by the expected overall beneficial effects on obesity-related metabolic abnormalities and cardiovascular risk factors. These parameters included waist circumference, blood pressure, lipids, and glucose metabolism.

Figure 27. Summary of QNEXA Benefits (Placebo-Subtracted Effect Size, 95% Confidence Interval)



BP=blood pressure; HbA1c=hemoglobin A1c; HDL=high-density lipoprotein; HOMA-IR=homeostasis model assessment of insulin resistance; HS-CRP=high-sensitivity C-reactive protein; IWQOL= Impact of Weight on Quality of Life; SF-36=Short-Form 36; TChol=total cholesterol.

8.1.2 Treatment Effects on Waist Circumference

Increased visceral or abdominal adiposity, independent of BMI, is associated with increased cardiovascular and mortality risk through a variety of mechanisms (Pischon 2008; Janssen 2004; Zhu 2002; Rexrode 1998). Waist circumference is a simple, convenient measure and serves as a surrogate for visceral abdominal adipose tissue, as it correlates with computed tomography- or magnetic resonance imaging-derived measurements of visceral fat content (Pi-Sunyer 2004). Accordingly, reductions in waist circumference, reflecting reductions in visceral adiposity, may be associated with an improved cardiovascular risk profile. Mean reductions in waist circumference of up to 13.9 cm were significantly greater with QNEXA treatment than with placebo.

8.1.3 Treatment Effects on Weight-Related Co-Morbidities

Drug-related improvements in co-morbidities were of the greatest magnitude in study OB-303, which by design included overweight and obese subjects who had two or more co-morbidities at baseline. The effects of QNEXA on the relevant disease markers and risk factors observed in the prespecified OB-303 co-morbidity subpopulations were numerically larger compared with the overall study population or the integrated cohorts. Moreover, the baseline upper quartile analyses, which included subjects with the highest degree of co-morbidities, demonstrated the greatest absolute drug effects. Taken together, the analyses of data from the different populations (study-specific and integrated ITT sets, co-morbidity subpopulations, and upper quartiles) support the conclusion that QNEXA is effective in promoting weight loss and health improvements across the spectrum of obesity and co-morbidity severity, and it is associated with more pronounced effects in subjects with more significant disease at baseline.

Treatment with QNEXA resulted in significant improvements in SBP and DBP relative to placebo. In the integrated analysis cohorts, treatment with both QNEXA Top and Mid dose resulted in significant improvements in SBP relative to placebo at both the Week 28 and Week 56 time points. QNEXA Top-dose treatment resulted in significant improvements in DBP relative to placebo at both Week 28 and Week 56, while QNEXA Mid-dose treatment resulted in significant improvements in DBP relative to placebo at Week 28 only. The overall effects on SBP and DBP were greatest in study OB-303, where the overall reductions in blood pressure were driven by the effects in approximately 50% of randomized subjects with hypertension at baseline. The largest mean reductions in blood pressure were observed in the subpopulation of subjects with hypertension and in subjects with baseline SBP and DBP in the upper quartiles of the study population. In addition, compared with placebo subjects, a higher proportion of QNEXA-treated subjects had reductions in the number of concomitant antihypertensive medications and a lower proportion had increases in concomitant antihypertensive medications. Had antihypertensive medication use been controlled during these trials, apparent differences between QNEXA and placebo may have been even larger.

Treatment with QNEXA also resulted in significant improvements in lipid parameters relative to placebo. In the integrated analysis cohorts, treatment with QNEXA Top and Mid dose resulted in significant improvements in TC and TG relative to placebo at both the Week 28 and Week 56 time points. Treatment with QNEXA Top and Mid dose resulted in significant improvements in HDL-C relative to placebo at Week 56. QNEXA Top-dose treatment resulted in significant improvements in LDL-C relative to placebo at both Week 28 and Week 56, while QNEXA Mid-dose treatment resulted in significant improvements in LDL-C relative to placebo at Week 28 only. Additionally, treatment with QNEXA Top and Mid dose resulted in clinically meaningful reductions in TG and increases in HDL-C, without increasing LDL-C in the subpopulation of subjects with hypertriglyceridemia at baseline in study OB-303. Consistent with other study-specific co-morbidity subpopulation results, subjects in study OB-303 with hypertriglyceridemia and baseline lipid values in the upper quartiles (or lower quartile for HDL-C) demonstrated the largest numerical changes in lipid parameters.

Effects on glycemic endpoints were observed in an overall population as demonstrated by the results of the integrated analyses; however, the most pronounced glycemic effects with QNEXA treatment were observed in diabetic and insulin-resistant prediabetic subjects. Treatment with QNEXA Top and Mid dose significantly reduced HbA_{1c} and fasting serum glucose relative to placebo at both the Week 28 and Week 56 time points.

The effects of QNEXA treatment on HbA_{1c} and fasting serum glucose were even greater in subjects with diabetes in studies OB-303 and DM-230 than in the 1-year cohort. The changes in HbA_{1c} and fasting serum glucose observed in the subpopulation of subjects with diabetes in study OB-303 were consistent with the results from the Phase 2 studies conducted in subjects with diabetes (study OB-202 and extensions DM-230 and DM-231). Notably, the mean baseline HbA_{1c} among the approximately 350 subjects with type 2 diabetes in study OB-303 was 6.8%, marking relatively good average glycemic control. In study OB-202, which enrolled obese subjects with type 2 diabetes, the mean baseline HbA_{1c} was 8.7%, and larger reductions in HbA_{1c} were observed at study endpoint for this population than for subjects with diabetes in study OB-303. Development of type 2 diabetes is generally preceded by an established pattern of hyperinsulinemia and increased insulin resistance. In the at-risk population treated in study OB-

303, QNEXA treatment resulted in clinically and statistically significant decreases in fasting insulin levels and insulin resistance as assessed by HOMA-IR, compared with placebo. As a result, among nondiabetic subjects treated in this study program, there was a statistically significant 41% reduction in the incidence of newly diagnosed type 2 diabetes in subjects treated with QNEXA compared to placebo. Taken together, the clinical trial data strongly support a benefit of QNEXA-associated weight loss on glycemic control in subjects with type 2 diabetes.

8.1.4 Treatment Effects on Biomarkers of Cardiovascular Disease Risk

Effects of treatment on biomarkers of cardiovascular disease risk, such as hs-CRP, adiponectin, and fibrinogen, were measured in study OB-303. Treatment with QNEXA Top and Mid dose resulted in statistically significant mean changes in hs-CRP, adiponectin, and fibrinogen. The magnitude of reduction in hs-CRP appears to be comparable to those observed in the JUPITER trial with rosuvastatin (Ridker 2008).

8.2 Risks of Treatment

The safety and tolerability profile of QNEXA should be evaluated in the context of the known adverse effects of the component agents when used as monotherapy for various indications. It is also important to recognize that the adverse effects observed with phentermine and topiramate monotherapy, which inform current labeling and publications, were generally observed in subjects treated with doses higher than those studied in the QNEXA clinical development program.

Phentermine, a sympathomimetic amine, acts through central nervous system stimulation. Central nervous system adverse events associated with its use include overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, and headache. Cardiovascular system events, including palpitations, tachycardia, and elevation of blood pressure, and gastrointestinal events, including dryness of the mouth, unpleasant taste, diarrhea, and constipation, are also described. The product label for phentermine has warnings related to a possible association with primary pulmonary hypertension and valvular heart disease. The latter complications occurred when phentermine was used in combination with fenfluramine or

dexfenfluramine. Numerous studies have provided conclusive epidemiologic, pharmacologic, and clinical evidence that the valvular effects were due to the fenfluramine or the dexfenfluramine component and not due to phentermine (Rothman 1999; Rothman 2000; Reeve 1999**)**.

Topiramate, is most commonly associated with adverse events related to the central nervous system. These adverse events include somnolence, fatigue, confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, mood disorders, and paresthesia related to its pharmacology as a carbonic anhydrase inhibitor.

From the integrated safety analyses of the QNEXA clinical program, the commonly observed adverse events associated with QNEXA treatment are known side effects of one or the other component agent and do not represent novel side effects engendered through the combined pharmacology of the two drugs. Furthermore, some of the expected side effects of topiramate, such as paresthesia, somnolence, psychomotor slowing, and difficulty with memory, occurred at a lower incidence with QNEXA treatment than cited in the product label for topiramate monotherapy. The lower incidence of these events may be due to the lower doses of topiramate in the fixed-dose combinations, the modified-release formulation of topiramate, or the oppositional pharmacodynamic effects of the phentermine component.

The safety results for the integrated 1-year cohort were similar to those for the integrated 6-month cohort, indicating that long-term QNEXA treatment did not result in any new types of adverse events or substantially increased rates of adverse events. In the 1-year cohort, the overall incidence of TEAEs was higher in the QNEXA dose groups than in the placebo group (placebo, 76.0%; Low dose, 80.0%; Mid dose, 85.1%; Top dose, 87.2%).

The most frequently reported TEAEs with QNEXA treatment were paresthesia (17.0%), dry mouth (16.6%), constipation (15.1%), upper respiratory tract infection (13.5%), nasopharyngitis (10.0%), and headache (9.8%).

The incidence of SAEs in the 1-year cohort was low and similar across the treatment groups (placebo, 3.3%; Low dose, 2.5%; Mid dose, 2.8%; Top dose, 3.6%). The incidence of cardiac

SAEs was not increased in QNEXA-treated subjects relative to placebo-treated subjects. The percentage of subjects who discontinued study drug due to a TEAE was higher in the QNEXA treatment groups than in the placebo group (placebo, 8.4%; Low dose, 11.3%; Mid dose, 11.6%; Top dose, 17.3%). Similar results were observed for the 6-month cohort.

QNEXA treatment was associated with a higher incidence of cognitive adverse events, although most of these events were mild in severity, none was serious, and discontinuations attributable to cognitive impairment were infrequent. The QNEXA Top- and Mid-dose groups showed a higher incidence of anxiety-related adverse events, and the QNEXA Top-dose group was associated with a higher incidence of depression adverse events. Importantly, mood-related adverse events were primarily mild in severity and none was serious. Study drug discontinuation for each of these TEAEs was <2%, and overall, there was no difference between the QNEXA groups and placebo with respect to the use of new antidepressant or psychiatric medications.

All treatment groups had mean decreases in the PHQ-9 total score, indicating overall improvement in the presence and severity of depression. No clinically important differences were observed among the treatment groups in mean changes in the PHQ-9 score. The summary of worsening shifts in PHQ-9 depression severity by treatment group likewise did not reveal any consistent treatment-related patterns. Therefore, with regard to PHQ-9-assessed depression, the effects of up to 56 weeks of treatment with QNEXA were not distinguishable on a population basis from those of placebo.

No differences were observed among the treatment groups in responses on the C-SSRS and PHQ-9 assessments of suicidal behavior and suicidal ideation. No subject in the 1-year cohort had a positive response to the C-SSRS composite measure at any time point after randomization. No significant differences were observed among the placebo group and the QNEXA groups regarding the incidence or emergence of suicidal behavior or suicidal ideation.

No clinically important differences were noted among the treatment groups in changes in safety laboratory parameters. In the individual studies, there were no important differences among the treatment groups in changes in physical examination findings at the final study visit. The percentage of subjects with new/abnormal findings on auscultation of the heart, such as abnormal

heart sounds and murmurs, were similar with QNEXA treatment and placebo treatment. Furthermore, the results from the thorough QT/QTc study (study OB-118) demonstrated that QNEXA treatment does not cause QT prolongation; and the echocardiographic data from study OB-201 showed that QNEXA treatment does not result in changes in heart valve morphology. The overall safety evaluation indicated no signal for cardiovascular risk with QNEXA treatment.

8.3 Benefit-Risk Conclusions

The data in this NDA show that treatment with QNEXA is highly effective for weight loss across a broad population of obese subjects, with a similarly broad range of obesity-related co-morbidities. Both by measures of central tendency and response rates for various degrees of weight loss from baseline, QNEXA treatment was markedly effective in a high proportion of subjects in promoting durable weight reduction and in ameliorating the course of obesity-related co-morbidities. The greatest weight-loss effects were observed among subjects with the highest baseline BMI, and the benefits of weight reduction with QNEXA treatment on cardiovascular, metabolic, and glycemic parameters were greatest for subjects with the most marked abnormalities at baseline.

Using the upper quartile of baseline values for various metabolic parameters, as defined by the population of subjects treated in OB-303, and the changes in these parameters in at-risk subjects after 1 year of treatment with QNEXA, the typical at-risk QNEXA patient can expect to achieve not only significant weight loss, but also clinically meaningful reductions in blood pressure, HbA_{1c}, LDL-C, and TG, and increases in HDL-C **(Table 42)**.

Table 42. Upper-Quartile Analysis of Cardiometabolic Risk Factors in Study OB-303

Parameter	Mean Baseline Upper Quartile Value	Post-Treatment Value on Top-Dose QNEXA
Blood pressure	147/92 mm Hg	126/81 mm Hg
HbA_{1c}	7.3%	6.7% (<ADA goal)
HDL-C	33 mg/dL	21% increase
LDL-C	171 mg/dL	18% decrease
TG	268 mg/dL	37% decrease

ADA=American Diabetes Association; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides.

QNEXA treatment was safe and generally well tolerated by overweight and obese subjects with and without weight-related co-morbidities. Several of the most commonly observed adverse events, notably paresthesia, dry mouth, dysgeusia, and insomnia, are well known and characterized side effects of one or the other component agent, and do not represent novel side effects engendered through the combined pharmacology of the two drugs. QNEXA treatment was associated with a higher incidence of insomnia, depression, anxiety and cognitive adverse events. However, the actual incidence rates were generally low, most of these events were mild in severity, none of these events was serious, and discontinuations were infrequent. These events generally occurred early on treatment, were manageable, and resolved without sequelae.

Current pharmacotherapies used in conjunction with diet and exercise can achieve modest weight loss in the range of 5%, while surgical interventions, which can achieve >15% weight loss, are invasive and often times result in postsurgical complications. The treatment gap between existing pharmacotherapies and surgical interventions is clear. Currently, there is no effective noninvasive treatment capable of achieving, in a broad population, a meaningful degree of weight loss of 10% with associated improvements on numerous cardiometabolic and inflammatory risk factors. QNEXA represents a significant advance in medical therapy for treatment of obesity and management of weight-related co-morbidities. For obese individuals, the adverse impact of obesity on health outcomes is well documented. Based on the results of the trials conducted in support of the NDA, among the high percentage of treated subjects who respond favorably to QNEXA treatment as part of a concerted weight management regimen, durable weight loss and substantial improvements in weight-related co-morbidities are expected to reduce the severity of or prevent the long-term health consequences of obesity. In conclusion, on the basis of extensive efficacy and safety data from clinical studies, QNEXA fixed combination of phentermine and topiramate has a favorable benefit/risk profile when used as an adjunctive measure in the management of obesity.

9 OPTIMAL CLINICAL USE OF QNEXA

QNEXA is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, and should be used only used in conjunction with nutrition and physical activity.

QNEXA is recommended for obese patients (BMI ≥30 kg/m^2), or overweight patients (BMI ≥27 kg/m^2) with such weight-related co-morbidities as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

Establish baseline weight and initiate QNEXA therapy with the lowest dose (3.75/23 mg) for 14 days. After 14 days and if tolerated, increase to the recommended dose (7.5/46 mg) for 90 days. Assess patient for weight loss and tolerability. Discontinue therapy if weight loss is <3% from baseline.

Continue QNEXA therapy at the recommended dose (7.5/46 mg) for an additional 90 days, and assess patient for weight loss and tolerability. Consider therapy with the maximum dose (15/92 mg) of QNEXA only if weight loss is <10% from baseline or if weight loss goal has not been attained. The maximum dose (15/92 mg) should be reached after 14 days of titration with the 11.25/69 mg dose.

A lower dose or discontinuation of QNEXA therapy should be considered at anytime during treatment if the patient experiences side effects or a lack of sufficient response.

In subjects with moderate renal impairment (CL_{cr} ≥30 to <50 mL/min) and severe renal impairment (CL_{cr} <30 mL/min), the maximum dose should not exceed 7.5/46 mg.

Patients should be counseled by their healthcare provider on following a nutritionally balanced dietary regimen, engaging in adequate physical activity, and on other lifestyle guidelines. Patients should eat only when hungry, and stop eating when full. A multivitamin may be recommended with QNEXA.

10 RISK EVALUATION AND MITIGATION STRATEGY

The Sponsor is submitting a Risk Evaluation and Mitigation Strategy (REMS) for QNEXA controlled-release formulation capsules in order to inform healthcare providers (HCPs) and patients of the potential risks associated with QNEXA and to mitigate the risks.

The specific objectives to be achieved by the QNEXA REMS are to inform and educate HCPs and patients about the following:

- The importance of appropriate and safe use of QNEXA, specifically
    - The potential for misuse and over-prescribing
    - Appropriate dosing and titration
    - Using QNEXA as part of weight management program that includes proper nutrition and physical activity
- The importance of appropriate patient selection
    - BMI >30 or >27 kg/m^2 in patients with co-morbidities
- The risk of depression, anxiety, suicidality, and changes in behavior/mood
- The risk of cognitive events such as attention (concentration) and memory difficulties
    - Caution in driving a car or operating heavy machinery when initiating QNEXA
- The risk of acute angle closure glaucoma
- The risk of metabolic acidosis
    - Concomitant therapy with another carbonic anhydrase inhibitor may increase the severity of metabolic acidosis and the risk of kidney stones
- The risks associated with pregnancy and messages around contraception
    - Females of childbearing potential must use adequate birth control
    - Discontinue QNEXA immediately if pregnancy occurs and contact HCP
        - Encourage those patients to register in the Weight Loss Drug Pregnancy Exposure Registry
    - QNEXA may make birth control pills less effective
    - Weight loss may increase fertility

10.1 REMS Design and Components

The REMS has been designed to communicate information to HCPs and patients by means of a Medication Guide, Communication Plan, and a Timetable for Assessments.

Medication Guide

The Medication Guide will be provided to patients with each dispensing of QNEXA. A Medication Guide will be packaged with each bottle of QNEXA. In addition, a tear-off pad of Medication Guides will be provided to all US pharmacies that dispense QNEXA. QNEXA is supplied in four strengths as (PHEN/TPM-CR) 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg capsules packaged in bottles of 30. QNEXA is a Schedule IV controlled substance, indicating it has a low potential for abuse, a currently accepted medical use, and a low chance for addiction or limited addictive properties. As a scheduled medication, patients will be restricted to 30 days of drug at each dispensing.

Packaging (primary and secondary) for all strengths of QNEXA will contain a prominent notice to the pharmacist to include a Medication Guide with each prescription in the event that less than a full bottle of QNEXA is prescribed. The statement will read, "Dispense the accompanying Medication Guide to each patient." Copies of the Medication Guide will be available through Sponsor sales representatives, the product website, www.qnexa.com, or by request through a QNEXA toll free information line (1-800-QNEXA).

Communication Plan

The Medication Guide and Communication Plan that support the REMS will educate patients and HCPs about

- The importance of appropriate and safe use of QNEXA, specifically
  - The potential for misuse and overprescribing
  - Appropriate dosing and titration
  - Using QNEXA as part of weight management program that includes proper nutrition and physical activity
- The importance of appropriate patient selection
  - BMI >30 or >27 kg/m^2 in patients with comorbidities
- The risk of depression, anxiety, suicidality, and changes in behavior/mood
- The risk of cognitive events such as attention (concentration) and memory difficulties

  - Caution in driving a car or operating heavy machinery when initiating QNEXA
- The risk of acute angle closure glaucoma
- The risk of metabolic acidosis
  - Concomitant therapy with another carbonic anhydrase inhibitor may increase the severity of metabolic acidosis and the risk of kidney stones
- The risks associated with pregnancy and messages around contraception
  - Females of childbearing potential must use adequate birth control
  - Discontinue QNEXA immediately if pregnancy occurs and contact HCP
    - Encourage those patients to register in the Weight Loss Drug Pregnancy Exposure Registry
  - QNEXA may make birth control pills less effective
  - Weight loss may increase fertility

The specific tools that will be used to communicate to HCPs and patients are outlined in **Appendix 9.**

REMS Assessment

The REMS includes a plan to assess both prescriber and patient understanding of the REMS messages. Knowledge, Attitude, and Behavior (KAB) surveys will be conducted with patients and prescribers in order to assess their comprehension of the serious risks of QNEXA as outlined in the REMS objectives listed above. The patient surveys will also measure pharmacy compliance with distribution of the QNEXA Medication Guide. The prescriber KAB surveys will include questions regarding the sources of HCP education. This information may assist in targeting areas for REMS enhancement should survey results indicate the need to improve communication of key REMS messages to ensure safe use of QNEXA. Should the data show that REMS goals and objectives as they relate to HCPs and patients are not being met, adjustments will be made to the educational materials and/or Medication Guide. Additionally, the evaluation will report on failures to adhere to distribution and dispensing requirements and corrective actions taken to address noncompliance.

The Sponsor will routinely monitor the HCP Training Program database. This database collects the names of HCPs who have participated in a comprehensive web-based education program about appropriate and safe use of QNEXA, obesity treatment and management, and the Weight Loss Drug Pregnancy Exposure Registry. The Sponsor will cross-check the names of the trained HCPs against current prescribers identified from IMS or other data sources, in an effort to educate prescribers who have not taken the training. Any prescribers who have not participated in the training will be sent a letter reminding them of the available web-based training and the importance of this education in managing patients on QNEXA.

The activities occurring under the REMS will be integrated with the Sponsor's routine pharmacovigilance program to ensure proper surveillance, monitoring, and reporting of AEs. The Sponsor's pharmacovigilance for this program will be enhanced to include the monitoring for adverse events of special interest. These will include all reports of depression, suicidality, changes in mood/behavior, cognition effects, acute angle closure glaucoma and pregnancy. The Sponsor's pharmacovigilance staff will collect as much information as possible about these events and will collect it in a standardized fashion using a form created for these specific events. The pharmacovigilance program will be implemented through standard operating procedures to ensure a robust, systematic process for capturing, evaluating, investigating, responding to, and reporting adverse events. Adverse event reports will be individually reviewed and collectively evaluated to determine if changes to the REMS messages could help to further mitigate the risks.

The Sponsor will participate in a voluntary, prospective Pregnancy Exposure Registry to estimate the risk of major birth defects and other adverse pregnancy outcomes among pregnant women exposed to QNEXA, or any other weight-loss treatment, at any time during pregnancy. Given the negative impact of obesity on pregnancy outcomes (increased cesarean deliveries, hypertensive disorders, miscarriages, macrosomia, shoulder dystocia, and congenital malformations), the comparison group will consist of pregnant women who are obese and not exposed to any weight-loss medications (Owens 2010). Patient educational tools, including the Medication Guide for QNEXA, will encourage patients to register with the Weight Loss Drug Pregnancy Exposure Registry if they become pregnant while taking QNEXA. HCP awareness of the pregnancy registry will be included in the REMS assessment reports to the FDA.

11 REFERENCES

Scientific publications have not been provided in the briefing document, but can be provided upon request.

Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763-778.

Adipex-P® [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2005.

Adipex-P® [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2006.

Astrup A, Caterson I, Zelissen P, et al. Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res.* 2004;12(10):1658-1669.

Bellisari, A. Evolutionary origins of obesity. *Obes Rev.* 2008;9(2):165-180.

Ben-Menachem E, Axelsen M, Johanson EH, Stagge A, Smith U. Predictors of weight loss in adults with topiramate-treated epilepsy. *Obes Res.* 2003;11(4):556-562.

Bray GA. Pharmacological treatment of obesity. In: Bouchard C, Bray GA, James WPT, eds. *Handbook of Obesity.* New York, NY: Marcel Dekker Inc.;1998:953-975.

Bray GA, Greenway FL. Current and potential drugs for treatment of obesity. *Endocr Rev.* 1999;20(6):805-875.

Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res.* 2003;11(6):722-733.

Centers for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *Morb Mortal Wkly Rep*. 1997;46(45):1061-1066.

Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. *Cochrane Database Syst Rev.* 2009; (2):CD003641.

Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *Int J Obes (Lond).* 2005;29(10):1153-1167.

Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA.* 2007;298(17):2028-2037.

Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA.* 2010;303(3):235-241.

Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB.Years of life lost due to obesity. *JAMA.* 2003;289(2):187-193.

Food and Drug Administration. Draft Guidance for Industry. Developing products for weight management. US Department of Health and Human Services, Center for Drug Evaluation and Research. February 2007.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Department of Health and Human Services. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. July 2009.

Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord.* 1992;16(6):397-415.

Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA.* 1999;282(16):1568-1575.

Jackson HC, Cheetham SC, Gregory PC, Antel J. Effect of chronic administration of topiramate and phentermine, alone and in combination, in an animal model of dietary-induced obesity. Presented at: Society for Neuroscience Annual Meeting. San Diego, CA; 2007. Poster 629.15/YY18.

Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr.* 2004;79(3):379-384.

Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. *Obes Rev.* 2003;4(4):257-290.

Meridia® [package insert]. North Chicago, IL: Abbott Laboratories; 2009.

Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature.* 1997;387(6636):903-908.

Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA.* 1999;282(16):1523-1529.

National Institutes of Health, US Department of Health and Human Services. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda, MD: National Institutes of Heath; 1998. NIH Publication 98-4083.

Owens LA, O'Sullivan EP, Kirwan B, Avalos G, Gaffney G, Dunne F; ATLANTIC DIP Collaborators. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care.* 2010;33(3):577-579.

Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet.* 2007;369(9555):71-77.

Pasanisi F, Contaldo F, de Simone G, Mancini M. Benefits of sustained moderate weight loss in obesity. *Nutr Metab Cardiovasc Dis.* 2001;11(6):401-406.

Picard F, Deshaies Y, Lalonde J, Samson P, Richard D. Topiramate reduces energy and fat gains in lean (Fa/?) and obese (fa/fa) Zucker rats. *Obes Res.* 2000;8(9):656-663.

Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008; 359(20):2105-2120.

Pi-Sunyer FX. The epidemiology of central fat distribution in relation to disease. *Nutr Rev.* 2004;62(7 Pt 2):S120-S126.

Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2006;113(6):898-918.

Reeve HL, Nelson DP, Archer SL, Weir EK. Effects of fluoxetine, phentermine, and venlafaxine on pulmonary arterial pressure and electrophysiology. *Am J Physiol.* 1999;276(2 Pt 1):L213-L219.

Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA.* 1998;280(21):1843-1848.

Richard D, Ferland J, Lalonde J, Samson P, Deshaies Y. Influence of topiramate in the regulation of energy balance. *Nutrition.* 2000;16(10):961-966.

Richard D, Picard F, Lemieux C, Lalonde J, Samson P, Deshaies Y. The effects of topiramate and sex hormones on energy balance of male and female rats. *Int J Obes Relat Metab Disord.* 2002;26(3):344-353.

Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.

Rothman RB, Ayestas MA, Dersch CM, Baumann MH. Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. *Circulation*. 1999;100(8):869-875.

Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation.* 2000;102(23):2836-2841.

Rothman RB, Baumann MH, Dersch CM, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001; 39(1):32-41.

Stenlöf K, Rossner S, Vercruysse F, Kumar A, Fitchet M, Sjöström L; OBDM-003 Study Group. Topiramate in the treatment of obese subjects with drug-naive type 2 diabetes. *Diabetes Obes Metab.* 2007;9(3):360-368.

Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. life expectancy. *N Engl J Med.* 2009;361(23):2252-2260.

Supuran CT, Di Fiore A, De Simone G. Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. *Expert Opin Emerg Drugs*. 2008;13(2):383-392.

Tonstad S, Tykarski A, Weissgarten J, et al. Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Cardiol.* 2005;96(2):243-251.

Topamax® [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2009.

Topiramate Summary Basis for Approval for Topamax NDA 20-505. Spring House, PA: The RW Johnson Pharmaceutical Research Institute; 1995**.**

White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. *Am J Hypertens.* 1999;12(2 Pt 2):50S-55S.

Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M; OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord.* 2004;28(11):1399-1410.

Withrow D, Alter DA. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. *Obes Rev.* 2010 Jan 27. [Epub ahead of print.] DOI: 10.1111/j.1467-789X.2009.00712.x. Accessed June 10, 2010.

Xenical® [package insert]. Nutley, NJ: Roche Laboratories, Inc.; 2009.

Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr.* 2002;76(4):743-749.

Zolkowska D, Rothman RB, Baumann MH. Amphetamine analogs increase plasma serotonin: implications for cardiac and pulmonary disease. *J Pharmacol Exp Ther.* 2006;318(2):604-610.

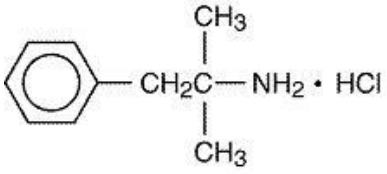
12 APPENDICES

12.1 Appendix 1: ADIPEX-P®, Topamax® Prescribing Information

ADIPEX-P - phentermine hydrochloride tablet
ADIPEX-P - phentermine hydrochloride capsule
TEVA PHARMACEUTICALS USA

DESCRIPTION

Phentermine hydrochloride USP has the chemical name of α,α,-Dimethylphenethylamine hydrochloride. The structural formula is as follows:



$C_{10}H_{15}N$ • HCl M.W. 185.7

Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder which is soluble in water and lower alcohols, slightly soluble in chloroform and insoluble in ether.

ADIPEX-P®, an anorectic agent for oral administration, is available as a capsule or tablet containing 37.5 mg of phentermine hydrochloride (equivalent to 30 mg of phentermine base).

ADIPEX-P® Capsules contain the inactive ingredients Corn Starch, Gelatin, Lactose Monohydrate, Magnesium Stearate, Titanium Dioxide, Black Iron Oxide, FD&C Blue #1, FD&C Red #40 and D&C Red #33.

ADIPEX-P® Tablets contain the inactive ingredients Corn Starch, Lactose (Anhydrous), Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, Sucrose, and FD&C Blue #1.

CLINICAL PHARMACOLOGY

ADIPEX-P® is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as “anorectics” or “anorexigenics.” It has not been established that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with “anorectic” drugs lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an “anorectic” drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drugs prescribed, such as the physician-investigator, the population treated and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks’ duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

INDICATIONS AND USAGE

ADIPEX-P® (phentermine hydrochloride)is indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).

Below is a chart of Body Mass Index (BMI) based on various heights and weights.

BMI is calculated by taking the patient’s weight, in kilograms (kg), divided by the patient’s height, in meters (m), squared. Metric conversions are as follows: pounds ÷ 2.2 = kg; inches x 0.0254 = meters.

BODY MASS INDEX (BMI), kg/m^2

Weight (pounds)	Height (feet, inches) 5'0"	5'3"	5'6"	5'9"	6'0"	6'3"
140	27	25	23	21	19	18
150	29	27	24	22	20	19
160	31	28	26	24	22	20
170	33	30	28	25	23	21
180	35	32	29	27	25	23
190	37	34	31	28	26	24
200	39	36	32	30	27	25
210	41	37	34	31	29	26
220	43	39	36	33	30	28
230	45	41	37	34	31	29
240	47	43	39	36	33	30
250	49	44	40	37	34	31

The limited usefulness of agents of this class (see **CLINICAL PHARMACOLOGY**) should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS

Advanced arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

ADIPEX-P® is indicated only as short-term monotherapy for the management of exogenous obesity. The safety and efficacy of combination therapy with phentermine and any other drug products for weight loss, including selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, fluvoxamine, paroxetine), have not been established. Therefore, coadministration of these drug products for weight loss is not recommended.
Primary Pulmonary Hypertension (PPH) – a rare, frequently fatal disease of the lungs – has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out; there have been rare cases of PPH in patients who reportedly have taken phentermine alone. The initial symptom of PPH is usually dyspnea. Other initial symptoms include: angina pectoris, syncope or lower extremity edema. Patients should be advised to report immediately any deterioration in exercise tolerance. Treatment should be discontinued in patients who develop new, unexplained symptoms of dyspnea, angina pectoris, syncope or lower extremity edema.
Valvular Heart Disease: Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The etiology of these valvulopathies has not been established and their course in individuals after the drugs are stopped is not known. The possibility of an association between valvular heart disease and the use of phentermine alone cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have taken phentermine alone.
Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

ADIPEX-P® may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

DRUG ABUSE AND DEPENDENCE

ADIPEX-P® is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of ADIPEX-P® should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.

Usage with Alcohol

Concomitant use of alcohol with ADIPEX-P® may result in an adverse drug interaction.

PRECAUTIONS

General

Caution is to be exercised in prescribing ADIPEX-P® (phentermine hydrochloride) for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of ADIPEX-P® and the concomitant dietary regimen.

ADIPEX-P® may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed with ADIPEX-P® (phentermine hydrochloride) to determine the potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with ADIPEX-P®. It is also not known whether ADIPEX-P® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ADIPEX-P® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular

Primary pulmonary hypertension and/or regurgitant cardiac valvular disease (see **WARNINGS**), palpitation, tachycardia, elevation of blood pressure.

Central Nervous System

Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely psychotic episodes at recommended doses.

Gastrointestinal

Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances.

Allergic

Urticaria.

Endocrine

Impotence, changes in libido.

OVERDOSAGE

Manifestations of acute overdosage with phentermine include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute phentermine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard. Acidification of the urine increases phentermine excretion. Intravenous phentolamine (Regitine®, CIBA) has been suggested for possible acute, severe hypertension, if this complicates phentermine overdosage.

DOSAGE AND ADMINISTRATION

Exogenous Obesity
Dosage should be individualized to obtain an adequate response with the lowest effective dose.
The usual adult dose is one capsule or tablet (37.5 mg) daily, administered before breakfast or 1-2 hours after breakfast. For tablets, the dosage may be adjusted to the patient's need. For some patients ½ tablet (18.75 mg) daily may be adequate, while in some cases it may be desirable to give ½ tablet (18.75 mg) two times a day.
Late evening medication should be avoided because of the possibility of resulting insomnia.
Phentermine is not recommended for use in patients sixteen (16) years of age and under.

HOW SUPPLIED
Available in tablets and capsules containing 37.5 mg phentermine hydrochloride (equivalent to 30 mg phentermine base). Each blue and white, oblong, scored tablet is debossed with "ADIPEX-P" and "9"-"9". The #3 capsule has an opaque white body and an opaque bright blue cap. Each capsule is imprinted with "ADIPEX-P" - "37.5" on the cap and two stripes on the body using dark blue ink.
Tablets are packaged in bottles of 30 (NDC 57844-009-56); 100 (NDC 57844-009-01); and 1000 (NDC 57844-009-10).
Capsules are packaged in bottles of 100 (NDC 57844-019-01).
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).
Manufactured for:
GATE PHARMACEUTICALS
Div. of Teva Pharmaceuticals USA
Sellersville, PA 18960
Manufactured by:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Rev. S 7/2005

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOPAMAX® safely and effectively. See full prescribing information for TOPAMAX®

TOPAMAX® (topiramate) TABLETS

TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

Initial U.S. Approval – 1996

----------RECENT MAJOR CHANGES----------

- Warnings and Precautions (5.3) [04/2009]
- Warnings and Precautions (5.8) [12/2009]

----------INDICATIONS AND USAGE----------

TOPAMAX® is an antiepileptic (AED) agent indicated for:

- Monotherapy epilepsy: Initial monotherapy in patients ≥10 years of age with partial onset or primary generalized tonic-clonic seizures (1.1).
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS) (1.2).
- Migraine: Treatment for adults for prophylaxis of migraine headache (1.3).

----------DOSAGE AND ADMINISTRATION----------

See DOSAGE AND ADMINISTRATION, Epilepsy: Adjunctive Therapy Use for additional details (2.1).

	Initial Dose	Titration	Recommended Dose
Epilepsy monotherapy: adults and pediatric patients ≥10 years (2.1)	50 mg/day in two divided doses	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day in two divided doses
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day in two divided doses
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	400 mg/day in two divided doses
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day in two divided doses
Migraine (2.3)	25 mg/day administered nightly for the first week	The dosage should be increased weekly by increments of 25 mg. Dose and titration should be guided by clinical outcome.	100 mg/day administered in two divided doses

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 25 mg, 50, mg, 100 mg, and 200 mg (3)
- Sprinkle Capsules: 15 mg and 25 mg (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Acute myopia and secondary angle closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible (5.1).
- Oligohidrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.2).
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.3).
- Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX® if clinically appropriate (5.4).
- Cognitive/neuropsychiatric: TOPAMAX® may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations (5.5).
- Withdrawal of AEDs: Withdrawal of TOPAMAX® should be done gradually (5.6).
- Hyperammonemia and encephalopathy associated with or without concomitant valproic acid use: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur (5.8).
- Kidney stones: Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided (5.9).

----------ADVERSE REACTIONS----------

The most common (≥5% more frequent than placebo or low dose topiramate in monotherapy) adverse reactions in controlled, epilepsy clinical trials were paresthesia, anorexia, weight decrease, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, difficulty with concentration/attention, and confusion. The most common (≥5% more frequent than placebo) adverse reactions in controlled, migraine clinical trials were paresthesia and taste perversion.

TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT ORTHO-MCNEIL NEUROLOGICS AT 1-800-526-7736 OR FDA AT 1-800-FDA-1088 OR *WWW.FDA.GOV/MEDWATCH.*

----------DRUG INTERACTIONS----------

Summary of antiepileptic drug (AED) interactions with TOPAMAX® (7.1).

AED Co-administered	AED Concentration	TOPAMAX Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
NE = Not Evaluated

- Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (5.7).
- Oral contraceptives: Decreased contraceptive efficacy and increased breakthrough bleeding should be considered, especially at doses greater than 200 mg/day (7.3).
- Metformin is contraindicated with metabolic acidosis, a possible effect of topiramate (7.4)
- Lithium levels should be monitored when co-administered with high-dose topiramate (7.5)
- Other Carbonic Anhydrase Inhibitors: monitor the patient for the appearance or worsening of metabolic acidosis (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Renal Impairment: In renally impaired patients (creatinine clearance less than 70 mL/min/1.73 m^2), one half of the adult dose is recommended (2.4).
- Patients Undergoing Hemodialysis: Topiramate is cleared by hemodialysis. Dosage adjustment is necessary to avoid rapid drops in topiramate plasma concentration during hemodialysis (2.6).
- Pregnancy: based on animal data, may cause fetal harm. To enroll in the North American Antiepileptic Drug Pregnancy Registry call 1-800-233-2334 (toll free) (8.1).
- Geriatric Use: Dosage adjustment may be necessary for elderly with impaired renal function (8.5).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved Medication Guide.

Revised: December 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures. Effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials *[see Clinical Studies (14.1)]*.

1.2 Adjunctive Therapy Epilepsy

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome *[see Clinical Studies (14.2)]*.

1.3 Migraine

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache *[see Clinical Studies (14.3)]*. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Epilepsy

In the controlled adjunctive (i.e., add-on) trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800 or 1,000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures.

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken.

TOPAMAX® can be taken without regard to meals.

Monotherapy Use

The recommended dose for topiramate monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. Approximately 58% of patients randomized to 400 mg/day achieved this maximal dose in the monotherapy controlled trial; the mean dose achieved in the trial was 275 mg/day. The dose should be achieved by titration according to the following schedule:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Adjunctive Therapy Use

Adults (17 Years of Age and Over) - Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial onset seizures is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Daily doses above 1,600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks *[see Clinical Studies (14.1)]*.

Pediatric Patients (Ages 2 - 16 Years) – Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy for pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2 week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than

in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks *[see Clinical Studies (14.1)]*.

2.2 Migraine

The recommended total daily dose of TOPAMAX® as treatment for adults for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is:

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

TOPAMAX® can be taken without regard to meals.

2.3 Administration of TOPAMAX® Sprinkle Capsules

TOPAMAX® (topiramate capsules) Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

2.4 Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

2.5 Geriatric Patients (Ages 65 Years and Over)

Dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate <70 mL/min/1.73 m^2) is evident *[see Clinical Pharmacology (12.3)]*.

2.6 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the

patient being dialyzed.

2.7 Patients with Hepatic Disease

In hepatically impaired patients, topiramate plasma concentrations may be increased. The mechanism is not well understood.

3 DOSAGE FORMS AND STRENGTHS

TOPAMAX® (topiramate) Tablets are available as debossed, coated, round tablets in the following strengths and colors:

25 mg cream (debossed “OMN” on one side; "25" on the other)

50 mg light-yellow (debossed “OMN” on one side; "50" on the other)

100 mg yellow (debossed “OMN” on one side; "100" on the other)

200 mg salmon (debossed “OMN” on one side; "200" on the other)

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off white spheres. The gelatin capsules are white and clear.

They are marked as follows:

15 mg capsule with “TOP” and “15 mg” on the side

25 mg capsule with “TOP” and “25 mg” on the side

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible,

according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

5.2 Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in pediatric patients. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

5.3 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including TOPAMAX®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk

of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing TOPAMAX® or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.4 Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been

observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet or specific drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in adults in the epilepsy controlled clinical trial for monotherapy was 15% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400 mg/day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg/day and 7% for 400 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (2-16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for TOPAMAX® (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX® and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

Although not approved for use in patients under 2 years of age with partial onset seizures, a controlled trial that examined this population revealed that topiramate produced a metabolic acidosis that is notably greater in magnitude than that observed in controlled trials in older children and adults. The mean treatment difference (25 mg/kg/d topiramate-placebo) was -5.9 mEq/L for bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate <20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/d, 50% for 15 mg/kg/d, and 45% for 25 mg/kg/d [*see Pediatric Use (8.4)*].

In pediatric patients (10 years up to 16 years of age), the incidence of persistent treatment-

emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 7% for 50 mg/day and 20% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in this trial was 4% for 50 mg/day and 4% for 400 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of infants/toddlers, with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in Z SCORES for length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal infants. Reductions in Z SCORES for length and weight were correlated to the degree of acidosis *[see Pediatric Use (8.4)]*.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

5.5 Cognitive/Neuropsychiatric Adverse Reactions

Adverse reactions most often associated with the use of TOPAMAX® were related to the central nervous system and were observed in both the epilepsy and migraine populations. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g. confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g. depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive-Related Dysfunction

The majority of cognitive-related adverse reactions were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these reactions. Many of these reactions contributed to withdrawal from treatment *[see Adverse Reactions (6)]*.

In the add-on epilepsy controlled trials (using rapid titration such as 100-200 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 42% for 200 mg/day, 41% for 400 mg/day, 52% for 600 mg/day, 56% for 800 and 1000 mg/day, and 14% for placebo. These dose-related adverse reactions began with a similar frequency in the titration or in the maintenance phase, although in some patients the events began during titration and persisted into the maintenance phase. Some patients who experienced one or more cognitive-related adverse reactions in the titration phase had a dose-related recurrence of these reactions in the maintenance phase.

In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for TOPAMAX® 50 mg/day and 26% for 400 mg/day.

In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day (the recommended dose), 28% for 200 mg/day, and 10% for placebo These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse reactions and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse reaction. The most common cognitive adverse reactions occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive reactions.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood) were dose-related for both the epilepsy and migraine populations [*see Warnings and Precautions (5.3)]*.

Somnolence/Fatigue

Somnolence and fatigue were the adverse reactions most frequently reported during clinical trials of TOPAMAX® for adjunctive epilepsy. For the adjunctive epilepsy population, the incidence of somnolence did not differ substantially between 200 mg/day and 1000 mg/day, but the incidence of fatigue was dose-related and increased at dosages above 400 mg/day. For the monotherapy epilepsy population in the 50 mg/day and 400 mg/day groups, the incidence of somnolence was dose-related (9% for the 50 mg/day group and 15% for the 400 mg/day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, fatigue and somnolence were dose-related and more common in the titration phase.

Additional nonspecific CNS events commonly observed with topiramate in the add-on epilepsy population include dizziness or ataxia.

Pediatric Patients

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies, the incidences of cognitive/neuropsychiatric adverse reactions in pediatric patients were generally lower than observed in adults. These reactions included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems and language problems. The most frequently reported neuropsychiatric reactions in pediatric patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported neuropsychiatric reactions in pediatric patients in the 50 mg/day and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

No patients discontinued treatment due to any adverse events in the adjunctive epilepsy double-blind trials. In the monotherapy epilepsy double-blind trial, 1 pediatric patient (2%) in the 50 mg/day group and 7 pediatric patients (12%) in the 400 mg/day group discontinued treatment due to any adverse events. The most common adverse reaction associated with discontinuation of therapy was difficulty with concentration/attention; all occurred in the 400 mg/day group.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including TOPAMAX® should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency *[see Clinical Studies (14)]*. In situations where rapid withdrawal of TOPAMAX® is medically required, appropriate monitoring is recommended.

5.7 Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure). This represents an incidence of 0.0035 deaths per patient year. Although this

rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

5.8 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)

Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs of adolescents (12-16 years) who were treated with topiramate monotherapy for migraine prophylaxis (incidence above normal, 22% for placebo, 26% for 50 mg/day, 41% for 100 mg daily) and in very young pediatric patients (1-24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10 % for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). Topiramate is not approved as monotherapy for migraine prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. In some patients, ammonia was markedly increased ($\geq$50% above upper limit of normal). In the adolescent patients, the incidence of markedly increased hyperammonemia was 6% for placebo, 6% for 50 mg, and 12% for 100 mg topiramate daily. The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials, and in an open-label, extension trial. Dose-related hyperammonemia was also observed in the extension trial in pediatric patients up to 2 years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid (VPA).

Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA)

Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction.

Although topiramate is not indicated for use in infants/toddlers (1-24 months) VPA clearly produced a dose-related increased in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term, extension trial in these very young, pediatric patients *[see Use in Specific Populations (8.4)]*.

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients taking topiramate with valproic acid (VPA).

The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with VPA.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

5.9 Kidney Stones

A total of 32/2,086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2 to 4 times greater than expected in a similar, untreated population. In the double-blind monotherapy epilepsy study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones that were diagnosed clinically or by sonogram. Topiramate is not approved for pediatric patients less than 2 years old *[see Pediatric Use (8.4)]*.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (e.g., zonisamide,

acetazolamide or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH *[see Warnings and Precautions (5.4)]*. The concomitant use of TOPAMAX® with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

5.10 Paresthesia

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®. Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials than in the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation.

5.11 Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function *[see Dosage and Administration (2)]*.

5.12 Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

5.13 Monitoring: Laboratory Tests

Topiramate treatment was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies.

Topiramate treatment causes non-anion gap, hyperchloremic, metabolic acidosis manifested by a decrease in serum bicarbonate and increase in serum chloride. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended *[see Warnings and Precautions (5.4)]*.

Controlled trials of adjunctive topiramate treatment of adults for partial onset seizures showed an increased incidence of markedly decreased serum phosphorus (6% topiramate, 2% placebo), markedly increased serum alkaline phosphatase (3% topiramate, 1% placebo), and decreased serum potassium (0.4 % topiramate, 0.1 % placebo). The clinical significance of these abnormalities has not been clearly established.

Changes in several clinical laboratory laboratories (increased creatinine, BUN, alkaline phosphatase, total protein, total eosinophil count and decreased potassium) have been observed in a clinical investigational program in very young (<2 years) pediatric patients who were treated with adjunctive topiramate for partial onset seizures [*see Pediatric Use (8.4)*].

Topiramate treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients (ages 12-16 years)who were treated for migraine prophylaxis in a double-blind, placebo-controlled study.

Topiramate treatment with or without concomitant valproic acid (VPA) can cause hyperammonemia with or without encephalopathy [*see Warnings and Precautions (5.8)]*.

6 ADVERSE REACTIONS

The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets.

6.1 Monotherapy Epilepsy

The adverse reactions in the controlled trial that occurred most commonly in adults in the 400 mg/day group and at a rate higher than the 50 mg/day group were: paresthesia, weight decrease, somnolence, anorexia, dizziness, and difficulty with memory NOS [see *Table 2*].

The adverse reactions in the controlled trial that occurred most commonly in children (10 years up to 16 years of age) in the 400 mg/day group and at a rate higher than the 50 mg/day group were: weight decrease, upper respiratory tract infection, paresthesia, anorexia, diarrhea, and mood problems [see *Table 3*].

Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. Adverse reactions associated with discontinuing therapy (>2%) included depression, insomnia, difficulty with memory (NOS), somnolence, paresthesia, psychomotor slowing, dizziness, and nausea.

Approximately 12% of the 57 pediatric patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. Adverse reactions associated with discontinuing therapy (>5%) included difficulty with concentration/attention.

The prescriber should be aware that these data cannot be used to predict the frequency of adverse reactions in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during the clinical study. Similarly, the cited frequencies cannot

be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse reactions incidences in the population studied.

Table 2: Incidence of Treatment-Emergent Adverse Reaction in the Monotherapy Epilepsy Trial in Adults[a] Where Incidence Was at Least 2% in the 400 mg/day Topiramate Group and Greater Than the Rate in the 50 mg/day Topiramate Group

	TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Reaction	50 (N= 160)	400 (N=159)
Body as a Whole-General Disorders		
Asthenia	4	6
Leg Pain	2	3
Chest Pain	1	2
Central & Peripheral Nervous System Disorders		
Paresthesia	21	40
Dizziness	13	14
Hypoaesthesia	4	5
Ataxia	3	4
Hypertonia	0	3
Gastro-Intestinal System Disorders		
Diarrhea	5	6
Constipation	1	4
Gastritis	0	3
Dry Mouth	1	3
Gastroesophageal Reflux	1	2
Liver and Biliary System Disorders		
Gamma-GT Increased	1	3
Metabolic and Nutritional Disorders		
Weight Decrease	6	16
Psychiatric Disorders		
Somnolence	9	15
Anorexia	4	14
Difficulty with Memory NOS	5	10
Insomnia	8	9
Depression	7	9
Difficulty with Concentration/Attention	7	8
Anxiety	4	6
Psychomotor Slowing	3	5
Mood Problems	2	5
Confusion	3	4
Cognitive Problem NOS	1	4
Libido Decreased	0	3
Reproductive Disorders, Female		
Vaginal Hemorrhage	0	3
Red Blood Cell Disorders		
Anemia	1	2
Resistance Mechanism Disorders		
Infection Viral	6	8
Infection	2	3

Respiratory System Disorders		
Bronchitis	3	4
Rhinitis	2	4
Dyspnea	1	2
Skin and Appendages Disorders		
Rash	1	4
Pruritus	1	4
Acne	2	3
Special Senses Other, Disorders		
Taste Perversion	3	5
Urinary System Disorders		
Cystitis	1	3
Renal Calculus	0	3
Urinary Tract Infection	1	2
Dysuria	0	2
Micturition Frequency	0	2

[a] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

Table 3: Incidence of Treatment-Emergent Adverse Reactions in the Monotherapy Epilepsy Trial in Pediatric Patients (Ages 10 up to 16 Years)[a] Where Incidence Was at Least 5% in the 400 mg/day Topiramate Group and Greater Than the Rate in the 50 mg/day Topiramate Group

	TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Reaction	50 (N=57)	400 (N=57)
Body as a Whole-General Disorders		
Fever	0	9
Central & Peripheral Nervous System Disorders		
Paresthesia	2	16
Gastro-Intestinal System Disorders		
Diarrhea	5	11
Metabolic and Nutritional Disorders		
Weight Decrease	7	21
Psychiatric Disorders		
Anorexia	11	14
Mood Problems	2	11
Difficulty with Concentration/Attention	4	9
Cognitive Problems NOS	0	7
Nervousness	4	5
Resistance Mechanism Disorders		
Infection Viral	4	9
Infection	2	7
Respiratory System Disorders		
Upper Respiratory Tract Infection	16	18
Rhinitis	2	7
Bronchitis	2	7
Sinusitis	2	5
Skin and Appendages Disorders		
Alopecia	2	5

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

6.2 Adjunctive Therapy Epilepsy

The most commonly observed adverse reactions associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia [see *Table 4*]. The most common dose-related adverse reactions at dosages of 200 to 1,000 mg/day were: fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease [see *Table 6]*.

Adverse reactions associated with the use of topiramate at dosages of 5 to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease [see *Table 7*].

In controlled clinical trials in adults, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse reactions. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. None of the pediatric patients who received topiramate adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse reactions.

Approximately 28% of the 1,757 adults with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse reactions; an individual patient could have reported more than one adverse reaction. These adverse reactions were: psychomotor slowing (4.0%), difficulty with memory (3.2%), fatigue (3.2%), confusion (3.1%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.7%), depression (2.6%), dizziness (2.5%), weight decrease (2.5%), nervousness (2.3%), ataxia (2.1%), and paresthesia (2.0%). Approximately 11% of the 310 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse reactions. Adverse reactions associated with discontinuing therapy included aggravated convulsions (2.3%),

difficulty with concentration/attention (1.6%), language problems (1.3%), personality disorder (1.3%), and somnolence (1.3%).

6.3 Incidence in Epilepsy Controlled Clinical Trials – Adjunctive Therapy – Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, and Lennox-Gastaut Syndrome

Table 4 lists treatment-emergent adverse reactions that occurred in at least 1% of adults treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse reactions during the first eight weeks of these trials no longer experienced them by their last visit. *Table 7* lists treatment-emergent adverse reactions that occurred in at least 1% of pediatric patients treated with 5 to 9 mg/kg topiramate in controlled trials that were numerically more common than in patients treated with placebo.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse reactions in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse reaction incidences in the population studied.

6.4 Other Adverse Reactions Observed During Double-Blind Epilepsy Adjunctive Therapy Trials

Other adverse reactions that occurred in more than 1% of adults treated with 200 to 400 mg of topiramate in placebo-controlled epilepsy trials but with equal or greater frequency in the placebo group were: headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, fever, diarrhea, vomiting, muscle weakness, insomnia, personality disorder, dysmenorrhea, upper respiratory tract infection, and eye pain.

Table 4: Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Adults[a,b] Where Incidence Was > 1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

		TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Reaction[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Body as a Whole-General Disorders			
Fatigue	13	15	30
Asthenia	1	6	3
Back Pain	4	5	3
Chest Pain	3	4	2
Influenza-Like Symptoms	2	3	4

Body System/ Adverse Reaction[c]	Placebo (N=291)	TOPAMAX® Dosage (mg/day) 200-400 (N=183)	600-1,000 (N=414)
Leg Pain	2	2	4
Hot Flushes	1	2	1
Allergy	1	2	3
Edema	1	2	1
Body Odor	0	1	0
Rigors	0	1	<1
Central & Peripheral Nervous System Disorders			
Dizziness	15	25	32
Ataxia	7	16	14
Speech Disorders/Related Speech Problems	2	13	11
Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language Problems	1	6	10
Coordination Abnormal	2	4	4
Hypoaesthesia	1	2	1
Gait Abnormal	1	3	2
Muscle Contractions Involuntary	1	2	2
Stupor	0	2	1
Vertigo	1	1	2
Gastro-Intestinal System Disorders			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal Pain	4	6	7
Constipation	2	4	3
Gastroenteritis	1	2	1
Dry Mouth	1	2	4
Gingivitis	<1	1	1
GI Disorder	<1	1	0
Hearing and Vestibular Disorders			
Hearing Decreased	1	2	1
Metabolic and Nutritional Disorders			
Weight Decrease	3	9	13
Muscle-Skeletal System Disorders			
Myalgia	1	2	2
Skeletal Pain	0	1	0
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1	2	1
Psychiatric Disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor Slowing	2	13	21
Difficulty with Memory	3	12	14
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Difficulty with Concentration/Attention	2	6	14
Mood Problems	2	4	9
Agitation	2	3	3
Aggressive Reaction	2	3	3
Emotional Lability	1	3	3
Cognitive Problems	1	3	3
Libido Decreased	1	2	<1
Apathy	1	1	3
Depersonalization	1	1	2
Reproductive Disorders, Female			
Breast Pain	2	4	0
Amenorrhea	1	2	2

Body System/ Adverse Reaction[c]	Placebo (N=291)	TOPAMAX® Dosage (mg/day) 200-400 (N=183)	600-1,000 (N=414)
Menorrhagia	0	2	1
Menstrual Disorder	1	2	1
Reproductive Disorders, Male			
Prostatic Disorder	<1	2	0
Resistance Mechanism Disorders			
Infection	1	2	1
Infection Viral	1	2	<1
Moniliasis	<1	1	0
Respiratory System Disorders			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Dyspnea	1	1	2
Skin and Appendages Disorders			
Skin Disorder	<1	2	1
Sweating Increased	<1	1	<1
Rash Erythematous	<1	1	<1
Special Sense Other, Disorders			
Taste Perversion	0	2	4
Urinary System Disorders			
Hematuria	1	2	<1
Urinary Tract Infection	1	2	3
Micturition Frequency	1	1	2
Urinary Incontinence	<1	2	1
Urine Abnormal	0	1	<1
Vision Disorders			
Vision Abnormal	2	13	10
Diplopia	5	10	10
White Cell and RES Disorders			
Leukopenia	1	2	1

[a] Patients in these add-on/ adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

[c] Adverse reactions reported by at least 1% of patients in the TOPAMAX® 200-400 mg/day group and more common than in the placebo group are listed in this table.

6.5 Incidence in Study 119 – Add-On Therapy– Adults with Partial Onset Seizures

Study 119 was a randomized, double-blind, add-on/adjunctive, placebo-controlled, parallel group study with 3 treatment arms: 1) placebo; 2) topiramate 200 mg/day with a 25 mg/day starting dose, increased by 25 mg/day each week for 8 weeks until the 200 mg/day maintenance dose was reached; and 3) topiramate 200 mg/day with a 50 mg/day starting dose, increased by 50 mg/day each week for 4 weeks until the 200 mg/day maintenance dose was reached. All patients were maintained on concomitant carbamazepine with or without another concomitant antiepileptic drug.

The incidence of adverse reactions (*Table 5)* did not differ significantly between the 2 topiramate regimens. Because the frequencies of adverse reactions reported in this study were markedly

lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies.

Table 5: Incidence of Treatment-Emergent Adverse Reactions in Study 119[a,b] Where Incidence Was ≥ 2% in the Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

		TOPAMAX® Dosage (mg/day)
Body System/ Adverse Reaction[c]	Placebo (N=92)	200 (N=171)
Body as a Whole-General Disorders		
Fatigue	4	9
Chest Pain	1	2
Cardiovascular Disorders, General		
Hypertension	0	2
Central & Peripheral Nervous System Disorders		
Paresthesia	2	9
Dizziness	4	7
Tremor	2	3
Hypoasthesia	0	2
Leg Cramps	0	2
Language Problems	0	2
Gastro-Intestinal System Disorders		
Abdominal Pain	3	5
Constipation	0	4
Diarrhea	1	2
Dyspepsia	0	2
Dry Mouth	0	2
Hearing and Vestibular Disorders		
Tinnitus	0	2
Metabolic and Nutritional Disorders		
Weight Decrease	4	8
Psychiatric Disorders		
Somnolence	9	15
Anorexia	7	9
Nervousness	2	9
Difficulty with Concentration/Attention	0	5
Insomnia	3	4
Difficulty with Memory	1	2
Aggressive Reaction	0	2
Respiratory System Disorders		
Rhinitis	0	4
Urinary System Disorders		
Cystitis	0	2
Vision Disorders		
Diplopia	0	2
Vision Abnormal	0	2

[a] Patients in these add-on/adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

[b] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

[c] Adverse reactions reported by at least 2% of patients in the TOPAMAX® 200 mg/day group and more common than in the placebo group are listed in this table.

Table 6: Incidence (%) of Dose-Related Adverse Reactions From Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[a]

	TOPAMAX® Dosage (mg/day)			
Adverse Reaction	Placebo (N = 216)	200 (N = 45)	400 (N = 68)	600 - 1,000 (N = 414)
Fatigue	13	11	12	30
Nervousness	7	13	18	19
Difficulty with Concentration/Attention	1	7	9	14
Confusion	4	9	10	14
Depression	6	9	7	13
Anorexia	4	4	6	12
Language problems	<1	2	9	10
Anxiety	6	2	3	10
Mood problems	2	0	6	9
Weight decrease	3	4	9	13

[a] Dose-response studies were not conducted for other adult indications or for pediatric indications.

Table 7: Incidence (%) of Treatment-Emergent Adverse Reaction in Placebo-Controlled, Add-On Epilepsy Trials in Pediatric Patients (Ages 2 -16 Years)[a,b] (Reaction that Occurred in at Least 1% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

Body System/ Adverse Reaction	Placebo (N=101)	Topiramate (N=98)
Body as a Whole - General Disorders		
Fatigue	5	16
Injury	13	14
Allergic Reaction	1	2
Back Pain	0	1
Pallor	0	1
Cardiovascular Disorders, General		
Hypertension	0	1
Central & Peripheral Nervous System Disorders		
Gait Abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech Disorders/Related Speech Problems	2	4
Hyporeflexia	0	2
Convulsions Grand Mal	0	1
Fecal Incontinence	0	1
Paresthesia	0	1
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva Increased	4	6
Constipation	4	5
Gastroenteritis	2	3
Dysphagia	0	1
Flatulence	0	1
Gastroesophageal Reflux	0	1
Glossitis	0	1
Gum Hyperplasia	0	1

Body System/ Adverse Reaction	Placebo (N=101)	Topiramate (N=98)
Heart Rate and Rhythm Disorders		
Bradycardia	0	1
Metabolic and Nutritional Disorders		
Weight Decrease	1	9
Thirst	1	2
Hypoglycemia	0	1
Weight Increase	0	1
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Hematoma	0	1
Prothrombin Increased	0	1
Thrombocytopenia	0	1
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14
Personality Disorder (Behavior Problems)	9	11
Difficulty with Concentration/Attention	2	10
Aggressive Reaction	4	9
Insomnia	7	8
Difficulty with Memory NOS	0	5
Confusion	3	4
Psychomotor Slowing	2	3
Appetite Increased	0	1
Neurosis	0	1
Reproductive Disorders, Female		
Leukorrhoea	0	2
Resistance Mechanism Disorders		
Infection Viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Respiratory Disorder	0	1
Skin and Appendages Disorders		
Skin Disorder	2	3
Alopecia	1	2
Dermatitis	0	2
Hypertrichosis	1	2
Rash Erythematous	0	2
Eczema	0	1
Seborrhoea	0	1
Skin Discoloration	0	1
Urinary System Disorders		
Urinary Incontinence	2	4
Nocturia	0	1
Vision Disorders		
Eye Abnormality	1	2
Vision Abnormal	1	2
Diplopia	0	1
Lacrimation Abnormal	0	1
Myopia	0	1

Body System/ Adverse Reaction	Placebo (N=101)	Topiramate (N=98)
White Cell and RES Disorders		
Leukopenia	0	2

[a] Patients in these add-on/adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

[b] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

6.6 Other Adverse Reactions Observed During All Epilepsy Clinical Trials

Topiramate has been administered to 2,246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo-controlled. During these studies, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reaction, similar types of reactions were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of patients who experienced a reaction of the type cited on at least one occasion while receiving topiramate. Reported reactions are included except those already listed in the previous tables or text, those too general to be informative, and those not reasonably associated with the use of the drug.

Reactions are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* syncope. *Infrequent*: abdomen enlarged. *Rare:* alcohol intolerance.

Cardiovascular Disorders, General: *Infrequent:* hypotension, postural hypotension, angina pectoris.

Central & Peripheral Nervous System Disorders: *Infrequent*: neuropathy, apraxia, hyperaesthesia, dyskinesia, dysphonia, scotoma, ptosis, dystonia, visual field defect, encephalopathy, EEG abnormal. *Rare:* upper motor neuron lesion, cerebellar syndrome, tongue paralysis.

Gastrointestinal System Disorders: *Infrequent:* hemorrhoids, stomatitis, melena, gastritis, esophagitis. *Rare:* tongue edema.

Heart Rate and Rhythm Disorders: *Infrequent:* AV block.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased.

Metabolic and Nutritional Disorders: *Infrequent:* dehydration, hypocalcemia, hyperlipemia, hyperglycemia, xerophthalmia, diabetes mellitus. *Rare:* hypernatremia, hyponatremia, hypocholesterolemia, creatinine increased.

Musculoskeletal System Disorders: *Frequent:* arthralgia. *Infrequent:* arthrosis.

Neoplasms: *Infrequent:* thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, pulmonary embolism.

Psychiatric Disorders: *Frequent:* impotence, hallucination, psychosis, suicide attempt. *Infrequent:* euphoria, paranoid reaction, delusion, paranoia, delirium, abnormal dreaming. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Skin and Appendages Disorders: *Infrequent:* urticaria, photosensitivity reaction, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Infrequent:* urinary retention, face edema, renal pain, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, strabismus. *Rare:* mydriasis, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia. *Rare:* lymphocytosis.

6.7 Migraine

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse reactions with topiramate were mild or moderate in severity. Most adverse reactions occurred more frequently during the titration period than during the maintenance period.

Table 8 includes those adverse reactions reported for patients in the placebo-controlled trials where the incidence in any topiramate treatment group was at least 2 % and was greater than that

for placebo patients.

Table 8: Incidence of Treatment-Emergent Adverse Reaction in Placebo-Controlled, Migraine Trials Where Incidence Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients [a]

		TOPAMAX® Dosage(mg/day)		
Body System/ Adverse Reaction	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Body as a Whole-General Disorders				
Fatigue	11	14	15	19
Injury	7	9	6	6
Asthenia	1	<1	2	2
Fever	1	1	1	2
Influenza-Like Symptoms	<1	<1	<1	2
Allergy	<1	2	<1	<1
Central & Peripheral Nervous System Disorders				
Paresthesia	6	35	51	49
Dizziness	10	8	9	12
Hypoaesthesia	2	6	7	8
Language Problems	2	7	6	7
Involuntary Muscle Contractions	1	2	2	4
Ataxia	<1	1	2	1
Speech Disorders/Related Speech Problems	<1	1	<1	2
Gastro-Intestinal System Disorders				
Nausea	8	9	13	14
Diarrhea	4	9	11	11
Abdominal Pain	5	6	6	7
Dyspepsia	3	4	5	3
Dry Mouth	2	2	3	5
Vomiting	2	1	2	3
Gastroenteritis	1	3	3	2
Hearing and Vestibular Disorders				
Tinnitus	1	<1	1	2
Metabolic and Nutritional Disorders				
Weight Decrease	1	6	9	11
Thirst	<1	2	2	1
Musculoskeletal System Disorders				
Arthralgia	2	7	3	1
Neoplasms				
Neoplasm NOS	<1	2	<1	<1
Psychiatric Disorders				
Anorexia	6	9	15	14
Somnolence	5	8	7	10
Difficulty with Memory NOS	2	7	7	11
Difficulty with Concentration/ Attention	2	3	6	10
Insomnia	5	6	7	6
Anxiety	3	4	5	6
Mood Problems	2	3	6	5
Depression	4	3	4	6
Nervousness	2	4	4	4
Confusion	2	2	3	4
Psychomotor Slowing	1	3	2	4

Body System/ Adverse Reaction	Placebo (N=445)	TOPAMAX® Dosage(mg/day) 50 (N=235)	100 (N=386)	200 (N=514)
Libido Decreased	1	1	1	2
Aggravated Depression	1	1	2	2
Agitation	1	2	2	1
Cognitive Problems NOS	1	<1	2	2
Reproductive Disorders, Female				
Menstrual Disorder	2	3	2	2
Reproductive Disorders, Male				
Ejaculation Premature	0	3	0	0
Resistance Mechanism Disorders				
Viral Infection	3	4	4	3
Otitis Media	<1	2	1	1
Respiratory System Disorders				
Upper Respiratory Tract Infection	12	13	14	12
Sinusitis	6	10	6	8
Pharyngitis	4	5	6	2
Coughing	2	2	4	3
Bronchitis	2	3	3	3
Dyspnea	2	1	3	2
Rhinitis	1	1	2	2
Skin and Appendages Disorders				
Pruritis	2	4	2	2
Special Sense Other, Disorders				
Taste Perversion	1	15	8	12
Taste Loss	<1	1	1	2
Urinary System Disorders				
Urinary Tract Infection	2	4	2	4
Renal Calculus	0	0	1	2
Vision Disorders				
Vision Abnormal	<1	1	2	3
Blurred Vision [b]	2	4	2	4
Conjunctivitis	1	1	2	1

[a] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

[b] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for > 50 % of reactions coded as vision abnormal, a preferred term.

Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse reactions, compared to 10% of the 445 placebo patients. The adverse reaction associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively.

Table 9 shows adverse reactions that were dose-dependent. Several central nervous system adverse reactions, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse reactions were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

Table 9: Incidence (%) of Dose-Related Adverse Reactions From Placebo-Controlled, Migraine Trials[a]

		TOPAMAX® Dosage (mg/day)		
Adverse Reaction	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Paresthesia	6	35	51	49
Fatigue	11	14	15	19
Nausea	8	9	13	14
Anorexia	6	9	15	14
Dizziness	10	8	9	12
Weight decrease	1	6	9	11
Difficulty with Memory NOS	2	7	7	11
Diarrhea	4	9	11	11
Difficulty with Concentration/ Attention	2	3	6	10
Somnolence	5	8	7	10
Hypoaesthesia	2	6	7	8
Anxiety	3	4	5	6
Depression	4	3	4	6
Mood Problems	2	3	6	5
Dry Mouth	2	2	3	5
Confusion	2	2	3	4
Involuntary Muscle Contractions	1	2	2	4
Abnormal Vision	<1	1	2	3
Renal Calculus	0	0	1	2

[a] The incidence of the adverse reaction in the 200 mg/day group was ≥ 2% than the incidence in both the placebo group and the 50 mg/day group.

6.8 Other Adverse Reactions Observed During Migraine Clinical Trials

Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse reactions that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials:

Body as a Whole: Pain, chest pain, allergic reaction.

Central & Peripheral Nervous System Disorders: Headache, vertigo, tremor, sensory disturbance, migraine aggravated.

Gastrointestinal System Disorders: Constipation, gastroesophageal reflux.

Musculoskeletal System Disorders: Myalgia.

Platelet, Bleeding, and Clotting Disorders: Epistaxis.

Reproductive Disorders, Female: Intermenstrual bleeding.

Resistance Mechanism Disorders: Infection, genital moniliasis.

Respiratory System Disorders: Pneumonia, asthma.

Skin and Appendages Disorders: Rash, alopecia.

Vision Disorders: Abnormal accommodation, eye pain.

6.9 Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving TOPAMAX® post-approval.

These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, and pemphigus.

7 DRUG INTERACTIONS

In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. *In vitro* studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. Drug interactions with some antiepileptic drugs, CNS depressants and oral contraceptives are described here. For other drug interactions, please refer to *Clinical Pharmacology (12.5)*.

7.1 Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. Concomitant administration of phenytoin or carbamazepine with topiramate decreased plasma concentrations of topiramate by 48% and 40%

respectively when compared to TOPAMAX® given alone *[see Clinical Pharmacology (12.5)]*.

In addition, concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy *[see Warnings and Precautions (5.8) or Clinical Pharmacology (12.5)]*.

7.2 CNS Depressants

Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

7.3 Oral Contraceptives

Exposure to ethinyl estradiol was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when TOPAMAX® was given as adjunctive therapy in patients taking valproic acid). However, norethindrone exposure was not significantly affected. In another pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [*see Clinical Pharmacology (12.5)]*.

7.4 Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated [*see Clinical Pharmacology (12.5)]*.

7.5 Lithium

In patients, lithium levels were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate *[see Clinical Pharmacology (12.5)]*.

7.6 Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if topiramate is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Topiramate may cause serious adverse fetal effects, based on pregnancy registry and nonclinical data. There are no adequate and well-controlled studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Pregnancy registry data suggest that there may be an association between the use of TOPAMAX® during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

In addition, data from these registries and other studies suggest that, compared with monotherapy, there may be an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.

In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Pregnancy Registry

The North American Drug Pregnancy Registry has been established to collect information and provide scientific knowledge about safety and outcomes associated with pregnant women being treated with antiepileptic drugs. It is desirable that the experience from patients who are exposed to topiramate during pregnancy be reported to this registry. Such information can be reported to the North American Drug Pregnancy Registry by either a healthcare provider or the patient by calling 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at *http://www.massgeneral.org/aed/*.

Topiramate treatment is associated with metabolic acidosis *[see Warnings and Precautions (5.4)]*. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state *[see Warnings and Precautions (5.4)]*. Newborns of mothers treated with topiramate should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. When oral doses of 20, 100 or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) 400 mg/day on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg

during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m^2 basis) and higher.

8.2 Labor and Delivery

Although the effect of TOPAMAX® on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor *[see Pregnancy (8.1)]*.

8.3 Nursing Mothers

Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when administered to a nursing woman.

8.4 Pediatric Use

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. In a single randomized, double-blind placebo-controlled investigational trial, the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in infants 1 to 24 months of age with refractory partial onset seizures, was assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg per day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile in this population was similar to that of older pediatric patients, although results from the above controlled study, and an open-label long-term extension study in these infants/toddlers (1 to 24 months old) suggested some adverse reactions/toxicities(not previously observed in older pediatric patients and adults; i.e, growth/length retardation, certain clinical laboratory abnormalities, and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been recognized previously from studies in older pediatric patients or adults for various indications.

These very young pediatric patients appeared to experience an increased risk for infections (any topiramate dose 12%, placebo 0%) and of respiratory disorders (any topiramate dose 40%, placebo 16%). The following adverse reactions were observed in at least 3% of patients on topiramate and were 3% to 7% more frequent then in patients on placebo: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and

bronchospasm. A generally similar profile was observed in older children *[see Adverse Reactions (6)]*.

Topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and protein (any topiramate dose 34%, placebo 6%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). This increased frequency of abnormal values was not dose-related. Creatinine was the only analyte showing a noteworthy increased incidence (topiramate 25 mg/kg/d 5%, placebo 0%) of a markedly abnormal increase *[see Warnings and Precautions (5.13)]*. The significance of these finding is uncertain.

Topiramate treatment also produced a dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10% for 5 mg/kg/d, 9% for 15 mg/kg/d, 14% for 25 mg/kg/d, and 11% for any topiramate dose *[see Warnings and Precautions (5.13)]*. There was a mean dose-related increase in alkaline phosphatase. The significance of these finding is uncertain.

Topiramate produced a dose-related increased incidence of treatment-emergent hyperammonemia *[see Warnings and Precautions (5.8)]*.

Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*.

In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.5)]*.

In this open-label, uncontrolled study, the mortality was 37 deaths/1000 patient years. It is not possible to know whether this mortality rate is related to topiramate treatment, because the background mortality rate for a similar, significantly refractory, young pediatric population (1-24 months) with partial epilepsy is not known.

Monotherapy Treatment in Partial Onset Epilepsy in Patients <10 Years Old

Safety and effectiveness in patients below the age of 10 years have not been established for the monotherapy treatment of epilepsy.

Migraine Prophylaxis in Pediatrics

Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache.

Topiramate treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients (ages 12-16 years) who were treated for migraine prophylaxis in a double-blind, placebo-controlled study. The incidence of these abnormal shifts was 4 % for placebo, 4 % for 50 mg, and 18 % for 100 mg *[see Warnings and Precautions (5.13)]*.

Juvenile Animal Studies

When topiramate (30, 90 or 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose, which is approximately 5-8 times the maximum recommended pediatric dose (9 mg/kg/day) on a body surface area (mg/m^2) basis.

8.5 Geriatric Use

In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate <70 mL/min/1.73 m^2) due to reduced clearance of topiramate *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.5)]*.

8.6 Race and Gender Effects

Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

8.7 Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). One-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.4)]*.

8.8 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account the duration of dialysis period, the clearance rate of the dialysis system being used, and the effective renal clearance of topiramate in the patient being dialyzed *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.4)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TOPAMAX® (topiramate) is not a controlled substance.

9.2 Abuse

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

9.3 Dependence

TOPAMAX® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®.

Topiramate overdose has resulted in severe metabolic acidosis *[see Warnings and Precautions (5.4)]*.

A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

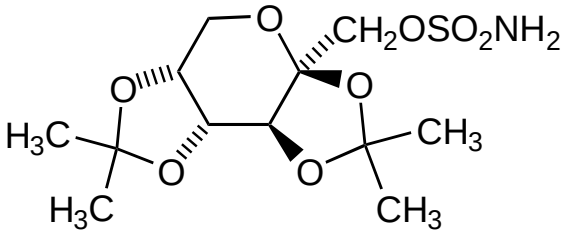
In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

11 DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. TOPAMAX® (topiramate) Tablets are

available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration. TOPAMAX® (topiramate capsules) Sprinkle Capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX®(topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (50, 100, and 200 mg tablets) and polysorbate 80.

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain topiramate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, sorbitan monolaurate, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

12.2 Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

12.3 Pharmacokinetics

The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 μg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 μg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

12.4 Special Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.4) and (2.5) and Warnings and Precautions (5.11)]*.

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required *[see Dosage and Administration (2.6)]*.

Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood *[see Dosage and Administration (2.7)]*.

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal

function in the elderly patient *[see Dosage and Administration (2.4) and Warnings and Precautions (5.11)]*.

Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

12.5 Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in the *Table 10*.

In *Table 10*, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 10: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.
TPM = Topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy *[see Warnings and Precautions (5.8) and Drug Interactions (7.1)]*.

CNS Depressants

Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants *[see Drug Interactions (7.2)]*.

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200 to 800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding *[see Drug Interactions (7.3)]*.

Digoxin

In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The

clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated.

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and AUC_{0-12h} increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear *[see Drug Interactions (7.4)]*.

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 22% decrease in C_{max} and 25% reduction in AUC_{24} for glyburide during topiramate administration. Systemic exposure (AUC) of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), was also reduced by 13% and 15%, reduced C_{max} by 18% and 25%, respectively. The steady-state pharmacokinetics of topiramate were

unaffected by concomitant administration of glyburide.

Lithium

In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate *[see Drug Interactions (7.5)]*.

Haloperidol

The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 males, 7 females).

Amitriptyline

There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 males; 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

Sumatriptan

Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 males, 10 females) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone

When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day, there was a reduction in risperidone (systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Coadministration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate, therefore this interaction is not likely to be of clinical significance.

Propranolol

Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 males, 17 females) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 males, 12 females) had no effect on the exposure to topiramate at a dose of 200 mg/day of topiramate.

Dihydroergotamine

Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Diltiazem

Co-administration of diltiazem (240 mg Cardizem CD®) with topiramate (150 mg/day) resulted in a10% decrease in C_{max} and 25% decrease in diltiazem AUC, 27% decrease in C_{max} and 18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Coadministration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine

Multiple dosing of topiramate (150 mg/day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg Effexor XR®) did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if topiramate is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis [*see Drug Interactions (7.5)*].

Drug/Laboratory Tests Interactions

There are no known interactions of topiramate with commonly used laboratory tests.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of

topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m^2 basis).

Mutagenesis

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

Impairment of Fertility

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m^2 basis).

14 CLINICAL STUDIES

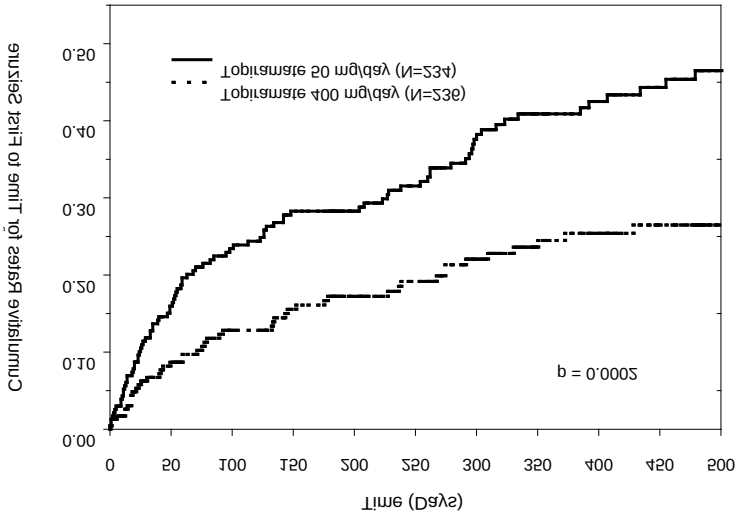
The studies described in the following sections were conducted using TOPAMAX® (topiramate) Tablets.

14.1 Monotherapy Epilepsy Controlled Trial

The effectiveness of topiramate as initial monotherapy in adults and children 10 years of age and older with partial onset or primary generalized seizures was established in a multicenter, randomized, double-blind, parallel-group trial.

The trial was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of subjects had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg/day or 400 mg/day. If the target dose could not be achieved, patients were maintained on the maximum tolerated dose. Fifty eight percent of patients achieved the maximal dose of 400 mg/day for >2 weeks, and patients who did not tolerate 150 mg/day were discontinued. The primary efficacy assessment was a between group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group (p=0.0002, log rank test; *Figure 1*). The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

Figure 1: Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure



Adjunctive Therapy Epilepsy Controlled Trials in Adults and Pediatric Patients (Ages 2 to 16 Years)

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 to 16 years with partial onset seizures was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® tablets or placebo. In this study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least six partial onset seizures, with or without secondarily generalized seizures, during the baseline phase were randomly assigned to placebo or TOPAMAX® tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg per day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225 or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Adjunctive Therapy Controlled Trial in Patients With Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing a single dosage of topiramate and placebo.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg per day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225 or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Adjunctive Therapy Controlled Trial in Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-

controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a 4-week baseline phase. Following baseline, patients were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg per day for a week; the dose was then increased to 3 mg/kg per day for one week then to 6 mg/kg per day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

Table 11: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[b]

		Target Topiramate Dosage (mg/day)					
Protocol	**Stabilization Dose**	**Placebo[a]**	**200**	**400**	**600**	**800**	**1,000**
YD	N	42	42	40	41	--	--
	Mean Dose	5.9	200	390	556	--	--
	Median Dose	6.0	200	400	600	--	--
YE	N	44	--	--	40	45	40
	Mean Dose	9.7	--	--	544	739	796
	Median Dose	10.0	--	--	600	800	1,000
Y1	N	23	--	19	--	--	--
	Mean Dose	3.8	--	395	--	--	--
	Median Dose	4.0	--	400	--	--	--
Y2	N	30	--	--	28	--	--
	Mean Dose	5.7	--	--	522	--	--
	Median Dose	6.0	--	--	600	--	--
Y3	N	28	--	--	--	25	--
	Mean Dose	7.9	--	--	--	568	--
	Median Dose	8.0	--	--	--	600	--
119	N	90	157	--	--	--	--
	Mean Dose	8	200	--	--	--	--
	Median Dose	8	200	--	--	--	--

[a] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3 and 119, 8 tablets/day; Protocol YE, 10 tablets/day.

[b] Dose-response studies were not conducted for other indications or pediatric partial onset seizures.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in *Table 12*. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 12: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Epilepsy Trials

Protocol	Efficacy Results	Placebo	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000	≈6 mg/kg/day*
Partial Onset Seizures								
Studies in Adults								
YD	N	45	45	45	46	--	--	--
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
	% Responders	18	24	44[d]	46[d]	--	--	--
YE	N	47	--	--	48	48	47	--
	Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	--
	% Responders	9	--	--	40[c]	41[c]	36[d]	--
Y1	N	24	--	23	--	--	--	--
	Median % Reduction	1.1	--	40.7[e]	--	--	--	--
	% Responders	8	--	35[d]	--	--	--	--
Y2	N	30	--	--	30	--	--	--
	Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
	% Responders	10	--	--	47[c]	--	--	--
Y3	N	28	--	--	--	28	--	--
	Median % Reduction	-20.6	--	--	--	24.3[e]	--	--
	% Responders	0	--	--	--	43[c]	--	--
119	N	91	168	--	--	--	--	--
	Median % Reduction	20.0	44.2[c]	--	--	--	--	--
	% Responders	24	45[c]	--	--	--	--	--
Studies in Pediatric Patients								
YP	N	45	--	--	--	--	--	41
	Median % Reduction	10.5	--	--	--	--	--	33.1[d]
	% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h]								
YTC	N	40	--	--	--	--	--	39
	Median % Reduction	9.0	--	--	--	--	--	56.7[d]
	% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]								
YL	N	49	--	--	--	--	--	46
	Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
	% Responders	14	--	--	--	--	--	28[g]
Improvement in Seizure Severity[j]		28	--	--	--	--	--	52[d]

Comparisons with placebo: [a] p=0.080; [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e] p=0.065; [f] p≤0.005;[g] p=0.071;
[h] Median % reduction and % responders are reported for PGTC Seizures;
[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures;
[j] Percent of subjects who were minimally, much, or very much improved from baseline

* For Protocols YP and YTC, protocol-specified target dosages (<9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of 6 mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day.

Subset analyses of the antiepileptic efficacy of TOPAMAX® tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

In clinical trials for epilepsy, daily dosages were decreased in weekly intervals by 50 to 100 mg per day in adults and over a 2 to 8 week period in children; transition was permitted to a new antiepileptic regimen when clinically indicated.

14.2 Migraine Prophylaxis

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of TOPAMAX® in the prophylactic treatment of migraine headache. The design of both trials (one study was conducted in the US and one study was conducted in the US and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society diagnostic criteria. Patients with a history of cluster headaches or basilar, ophthalmoplegic, hemiplegic or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2-week washout of any prior migraine preventive medications before starting the baseline phase.

Patients who experienced 3 to 12 migraine headaches over the 4-weeks in the baseline phase were equally randomized to either TOPAMAX® 50 mg/day, 100 mg/day, 200 mg/day or placebo and treated for a total of 26 weeks (8-week titration period and 18-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25 mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily).

Effectiveness of treatment was assessed by the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate from the baseline phase to double-blind treatment period in each TOPAMAX® treatment group compared to placebo in the intent to treat (ITT) population.

In the first study, a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47.8 mg/day, 88.3 mg/day, and 132.1 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache frequency from baseline to the double-blind phase was -1.3, -2.1, and -2.2 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus -0.8 in the placebo group (see Figure 2). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant ($p<0.001$ for both comparisons).

In the second study, a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 46.5 mg/day, 85.6 mg/day, and 150.2 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200

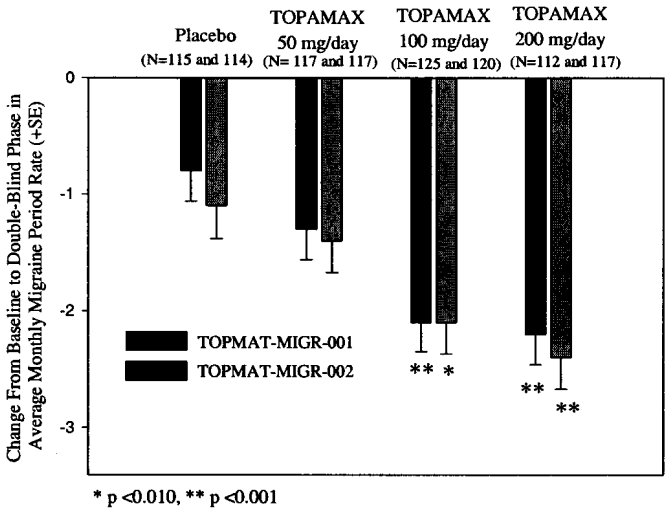
mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus -1.1 in the placebo group (see *Figure 2*). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant (p=0.008 and <0.001, respectively).

In both studies, there were no apparent differences in treatment effect within age or gender, subgroups. Because most patients were Caucasian, there were insufficient numbers of patients from different races to make a meaningful comparison of race.

For patients withdrawing from TOPAMAX®, daily dosages were decreased in weekly intervals by 25 to 50 mg per day.

Figure 2: Reduction in 4-Week Migraine Headache Frequency
(Studies TOPMAT-MIGR-001 and TOPMAT-MIGR-002)



16 HOW SUPPLIED/STORAGE AND HANDLING

TOPAMAX® Tablets

TOPAMAX® (topiramate) Tablets are available as debossed, coated, round tablets in the following strengths and colors:

25 mg cream tablet (debossed “OMN” on one side; "25" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-639-65)

50 mg light yellow tablet (debossed “OMN” on one side; "50" on the other) and are available in

bottles of 60 count with desiccant (NDC 50458-640-65)

100 mg yellow tablet (debossed “OMN” on one side; "100" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-641-65)

200 mg salmon tablet (debossed “OMN” on one side; "200" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-642-65)

TOPAMAX® Sprinkle Capsules

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off white spheres. The gelatin capsules are white and clear and are marked as follows:

15 mg capsule with “TOP” and “15 mg” on the side and are available in bottles of 60 (NDC 50458-647-65)

25 mg capsule with “TOP” and “25 mg” on the side and are available in bottles of 60 (NDC 50458-645-65)

Storage and Handling

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature (59° to 86°F, 15° to 30°C). Protect from moisture.

TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Patients and their caregivers should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking TOPAMAX®. Patients should be instructed to take TOPAMAX® only as prescribed. See FDA approved Medication Guide.

17.1 Eye Disorders

Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision, visual disturbances or periorbital pain *[see Warnings and Precautions (5.1)]*.

17.2 Oligohydrosis and Hyperthermia

Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather *[see Warnings and Precautions (5.2)]*.

17.3 Suicidal Behavior and Ideation

Patients, their caregivers, and families should be counseled that AEDs, including Topamax, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

17.4 Metabolic Acidosis

Patients should be warned about the potential, significant risk for metabolic acidosis that may be asymptomatic and may be associated with adverse effects on kidneys (e.g., kidney stones, nephrocalcinosis), bones (e.g., osteoporosis, osteomalacia, and/or rickets in children), and growth (e.g., growth delay/retardation) in pediatric patients *[see Warnings and Precautions (5.4)]*.

17.5 Interference with Cognitive and Motor Performance

Patients should be warned about the potential for somnolence, dizziness, confusion, difficulty concentrating, visual effects and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental performance, motor performance, and/or vision *[see Warnings and Precautions (5.5)]*.

Even when taking TOPAMAX® or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Therefore, all patients taking TOPAMAX® for epilepsy should be told to exercise appropriate caution when engaging in any activities where loss of consciousness could result in serious danger to themselves or those around them (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Physicians should discuss the appropriate level of caution with their patients, before patients with epilepsy engage in such activities.

17.6 Hyperammonemia and Encephalopathy

Patients should be warned about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. This hyperammonemia and encephalopathy can develop with topiramate treatment alone or with topiramate treatment with concomitant valproic acid (VPA).

Patients should be instructed to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status *[see Warnings and Precautions (5.8)]*.

17.7 Kidney Stones

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation *[see Warnings and Precautions (5.9)]*.

17.8 Use in Pregnancy

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy and to notify their physician if they are breastfeeding or intend to breastfeed during therapy with TOPAMAX® *[see Use in Specific Populations (*8.1*) and (*8.3*)]*.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. The registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number, 1-888-233-2334 *[see Use in Specific Populations (*8.1*)]*.

Manufactured by: Janssen Ortho, LLC Gurabo, Puerto Rico 00778

Manufactured for: Ortho-McNeil Neurologics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

[Insert component code]

Revised December 2009

MEDICATION GUIDE

TOPAMAX® (Toe-pa-max)
(topiramate)
Tablets and Sprinkle Capsules

Read this Medication Guide before you start taking TOPAMAX® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about TOPAMAX®, talk to your healthcare provider or pharmacist.

What is the most important information I should know about TOPAMAX®?

- **TOPAMAX® may cause eye problems.** Serious eye problems include:
  - any sudden decrease in vision with or without eye pain and redness,
  - a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).
  - These eye problems can lead to permanent loss of vision if not treated. You should call your healthcare provider right away if you have any new eye symptoms.
- **TOPAMAX® may cause decreased sweating and increased body temperature (fever).** People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition
- **Like other antiepileptic drugs, TOPAMAX® may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Do not stop TOPAMAX® without first talking to a healthcare provider.

- Stopping TOPAMAX® suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What is TOPAMAX®?

TOPAMAX® is a prescription medicine used:

- to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people 10 years and older,
- with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older,
- to prevent migraine headaches in adults.

What should I tell my healthcare provider before taking TOPAMAX®?

Before taking TOPAMAX®, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems, kidney stones or are getting kidney dialysis
- have a history of metabolic acidosis (too much acid in the blood)
- have liver problems
- have osteoporosis, soft bones, or decreased bone density
- have lung or breathing problems
- have eye problems, especially glaucoma
- have diarrhea
- have a growth problem
- are on a diet high in fat and low in carbohydrates, which is called a ketogenic diet
- are having surgery
- are pregnant or plan to become pregnant. It is not known if TOPAMAX® will harm your unborn baby. If you become pregnant while taking TOPAMAX®, talk to your healthcare

provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

- are breastfeeding. It is not known if TOPAMAX® passes into breast milk and if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take TOPAMAX®.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TOPAMAX® and other medicines may affect each other causing side effects.

Especially, tell your healthcare provider if you take:

- Valproic acid (DEPAKENE®, DEPAKOTE®)
- any medicines that impair or decrease your thinking, concentration, or muscle coordination.
- birth control pills. TOPAMAX® may make your birth control pills less effective. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and TOPAMAX®.

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take TOPAMAX®?

- Take TOPAMAX® exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- TOPAMAX® tablets should be swallowed whole. Do not chew the tablets. They may leave a bitter taste.
- TOPAMAX® sprinkle capsules may be swallowed whole or may be opened and sprinkled on a teaspoon of soft food. Drink fluids right after eating the food and medicine mixture to make sure it is all swallowed.
- Do not store any medicine and food mixture for later use.
- TOPAMAX® can be taken before, during, or after a meal. Drink plenty of fluids during the day. This may help prevent kidney stones while taking TOPAMAX®.
- If you take too much TOPAMAX®, call your healthcare provider or poison control center right away or go to the nearest emergency room.

- If you miss a single dose of TOPAMAX®, take it as soon as you can. However, if you are within 6 hours of taking your next scheduled dose, wait until then to take your usual dose of TOPAMAX®, and skip the missed dose. Do not double your dose. If you have missed more than one dose, you should call your healthcare professional for advice.
- Do not stop taking TOPAMAX® without talking to your healthcare provider. Stopping TOPAMAX® suddenly may cause serious problems. If you have epilepsy and you stop taking TOPAMAX® suddenly, you may have seizures that do not stop. Your healthcare provider will tell you how to stop taking TOPAMAX® slowly.
- Your healthcare provider may do blood tests while you take TOPAMAX®.

What should I avoid while taking TOPAMAX®?

- Do not drink alcohol while taking TOPAMAX®. TOPAMAX® and alcohol can affect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate heavy machinery until you know how TOPAMAX® affects you. TOPAMAX® can slow your thinking, motor skills, and/or vision.

What are the possible side effects of TOPAMAX®?

TOPAMAX® may cause serious side effects including:

See "What is the most important information I should know about TOPAMAX®?"

- **Metabolic Acidosis**. Metabolic acidosis can cause:
  - tiredness
  - loss of appetite
  - irregular heartbeat
  - impaired consciousness
- **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when TOPAMAX® is taken with a medicine called valproic acid (DEPAKENE® and DEPAKOTE®).
- **Kidney stones.** Drink plenty of fluids when taking TOPAMAX® to decrease your chances of getting kidney stones.
- **Effects on Thinking and Alertness.** TOPAMAX® may affect how you think, and cause confusion, problems with concentration, attention, memory, or speech. TOPAMAX® may cause depression or mood problems, tiredness, and sleepiness.
- **Dizziness or Loss of Muscle Coordination.**

Call your healthcare provider right away if you have any of the symptoms above.

The most common side effects of TOPAMAX® include:

- tingling of the arms and legs (paresthesia)
- not feeling hungry
- nausea
- a change in the way foods taste
- diarrhea
- weight loss
- nervousness
- upper respiratory tract infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of TOPAMAX®. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TOPAMAX®?

- Store TOPAMAX® tablets at room temperature, 59°F to 86°F (15°C to 30°C).
- Store TOPAMAX®® Sprinkle Capsules at or below 25°C (77°F).
- Keep TOPAMAX® in a tightly closed container.
- Keep TOPAMAX® dry and away from moisture.
- **Keep TOPAMAX® and all medicines out of the reach of children.**

General information about TOPAMAX®.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TOPAMAX® for a condition for which it was not prescribed. Do not give TOPAMAX® to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about TOPAMAX®. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TOPAMAX® that is written for health professionals.

For more information, go to www.topamax.com or call 1-800-526-7736.

What are the ingredients in TOPAMAX?

Active ingredient: topiramate

Inactive ingredients:

- **Tablets** - lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide and polysorbate 80.
- **Sprinkle Capsules** - sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, sorbitan monolaurate, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

Manufactured by: Janssen Ortho, LLC Gurabo, Puerto Rico 00778

Manufactured for: Ortho-McNeil Neurologics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

This Medication Guide has been approved by the U.S. Food and Drug Administration.

[Insert component code]

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12.2 Appendix 2: FDA Guidance for Industry

Guidance for Industry

Developing Products for Weight Management

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Eric Colman at 301-796-1190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2007
Clinical/Medical

Revision 1

Guidance for Industry

Developing Products for Weight Management

Additional copies are available from:

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Guidance for Industry[1]
Developing Products for Weight Management

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics (hereafter *products*) regulated within the Center for Drug Evaluation and Research (CDER) in the Food and Drug Administration (FDA) for the indication of weight management. This guidance applies to products intended to be used for medical weight loss, which can be defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c. This guidance revises the draft *Guidance for the Clinical Evaluation of Weight-Control Drugs* that issued in September 1996. When finalized, this guidance will replace the September 1996 draft guidance.

The September 1996 draft guidance is being revised to provide advice on conducting studies to evaluate the efficacy and safety of products for weight management in patients with medication-induced weight gain and weight management in obese pediatric patients. Recommendations on the design of studies evaluating the efficacy and safety of combinations of weight-management products are also provided.

This guidance does not explicitly discuss indications for weight loss or maintenance of lost weight (which also can be described as prevention of weight regain); however, weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management. Thus, the weight management indication incorporates and signifies weight loss and weight maintenance.

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

This guidance also does not discuss the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In January 2004, the FDA issued a notice in the *Federal Register* requesting public comment on the September 1996 draft guidance for the purpose of incorporating the latest scientific and clinical advances in weight management drug development. In September 2004, the FDA convened an advisory committee meeting to discuss the public comments received and to identify specific scientific, clinical, and regulatory issues that should be included in an updated guidance.

As a result, this revised guidance discusses several key areas of interest that are not covered in the September 1996 draft guidance. These areas include recommendations on the development of products for weight management in pediatric patients and in patients with medication-induced weight gain, and recommendations on the development of combinations of weight-management products.

III. OVERWEIGHT AND OBESITY CLINICAL BACKGROUND

A. The Adult Population

Obesity is a chronic, relapsing health risk defined by excess body fat. The pathogenesis of obesity involves the interaction of genetic, environmental, and behavioral factors. Total body fat can be accurately measured using hydrodensitometry and dual-energy x-ray absorptiometry (DEXA). Because body mass index (BMI), expressed as kilograms of weight divided by height in meters squared (kg/m^2), is simple and inexpensive to calculate, and correlates strongly with total body fat in non-elderly adults, it is commonly used as a surrogate for total body fat.

Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers (Caterson and Hubbard et al. 2004; Calle and Thun et al. 1999). The relationships between BMI and risks for death and major comorbidities vary by age, sex, race, and smoking status, but, in general, are lowest in individuals with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a curvilinear or linear manner with BMIs of 25 kg/m^2 to approximately 40 kg/m^2.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

Based on data relating BMI to mortality risk, the World Health Organization in 1995 and the National Institutes of Health in 1998 adopted the weight classifications by BMI that are shown in Table 1 (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998).

Table 1. Weight Classification Guidelines

Classification	**BMI**
Underweight	< 18.5 kg/m^2
Normal weight	18.5 kg/m^2 – 24.9 kg/m^2
Overweight	25 kg/m^2 – 29.9 kg/m^2
Obesity (class 1)	30 kg/m^2 – 34.9 kg/m^2
Obesity (class 2)	35 kg/m^2 – 39.9 kg/m^2
Extreme obesity (class 3)	$\geq$ 40 kg/m^2

An increased level of visceral or intra-abdominal adiposity, independent of BMI, increases the risk for metabolic derangements and perhaps cardiovascular disease (Janssen and Katzmarzyk et al. 2004; Rexrode and Carey et al. 1998; Zhu and Wang et al. 2002). Visceral fat content can be accurately measured with computed tomography (CT) or magnetic resonance imaging (MRI). Waist circumference, like BMI, is inexpensive and easy to measure and correlates with CT- and MRI-derived measurements of visceral fat content (Pi-Sunyer 2004). In general, a waist circumference greater than 40 inches (greater than 102 cm) in men and greater than 35 inches (greater than 88 cm) in women is accepted as indicating increased visceral adiposity (The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 2000).

In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005).

Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, at the time of this writing, there are no data from randomized, controlled trials on the effects of drug-induced weight loss on these clinical outcomes (Parker and Folsom 2003; Eilat-Adar and Eldar et al. 2004; Gregg and Gerzoff et al. 2003).

Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.

Patients with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities historically have been considered appropriate populations for treatment with weight-management medications (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998). Although these patient-selection criteria are to a degree arbitrary, and an argument may be made for criteria that are more or less restrictive, we believe that individuals with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products.

B. The Pediatric Population

As in adults, BMI correlates with more direct measures of adiposity in children and adolescents (American Academy of Pediatrics 2003; Barlow and Dietz 1998; Dietz and Robinson 2005; Speiser and Rudolf et al. 2005). Also similar to adults, BMI correlates with obesity-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus in pediatric patients.

In contrast to adults, the terms overweight and obese are used synonymously in pediatric patients (American Academy of Pediatrics 2003). The American Academy of Pediatrics (AAP) defines a pediatric-aged patient with an age- and sex-matched BMI of greater than or equal to 95th percentile as overweight or obese.

For patients aged 2 to 7 years, the AAP recommends weight loss through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex with the presence of one or more comorbidities. For patients who are 7 years of age or older, weight loss through lifestyle modification is recommended if the BMI is between the 85th and 95th percentile for age and sex with the presence of one or more comorbidities or if the BMI is greater than or equal to the 95th percentile for age and sex regardless of the presence of comorbidities.

Before therapeutic intervention, pediatric patients should receive a medical assessment to identify genetic (e.g., Prader-Willi syndrome) or endocrinologic (e.g., Cushing's syndrome) causes of their obesity. Patients also should be screened for the presence of comorbidities such as hypertension, glucose intolerance, and dyslipidemia.

The use of weight-management products in pediatric patients, as in adults, should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the expected benefits of weight loss are believed to outweigh the known and unknown risks of treatment with a particular weight-management product. Such a population might include obese pediatric patients with weight-related comorbidites.

IV. CLINICAL ASSESSMENT OF WEIGHT-MANAGEMENT PRODUCTS IN ADULT PATIENTS

A. Phase 1 and Phase 2 Trials

Before initiating phase 3 clinical trials, the pharmacokinetics and dose-response profiles of a new weight-management product should be well-characterized. Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m^2 to 35 kg/m^2) (Cheymol 2000). To increase the likelihood of identifying the most appropriate dose for the pivotal clinical trials, early phase clinical studies should include a range of doses and be designed to identify no-effect and maximally tolerated doses. Studies should be designed to differentiate the efficacy of all the active doses versus placebo. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. Forethought should be given to whether the product will be ultimately used in a fixed-dose or dose-titration scheme, as this dosing decision will also influence the size and duration of the studies.

Patients included in the early phase efficacy and safety studies generally should have BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by comorbidities. The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight. The effects by dose of the weight-management product on common weight-related comorbidities also should be examined and taken into account when choosing the most appropriate dose for the phase 3 studies.

B. Phase 3 Clinical Trials

1. Trial Design and Patient Populations

In general, phase 3 clinical trials examining the efficacy and safety of weight-management products should be randomized, double-blind, and placebo-controlled. The lifestyle modification programs used in the preapproval trials should be applicable to individual patients prescribed the product post-approval (i.e., programs should strike an appropriate balance between effectiveness and simplicity).

In general, patients should have or be at significant risk for weight-related morbidity and mortality. Such patients include those with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease).

Effort should be made to include in the studies a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest. Development programs also should include a representative sample of patients with extreme obesity (BMI greater than 40 kg/m^2).

2. Trial Size and Duration

The number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety. A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.

For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo group (i.e., 4.5 percent versus 3 percent). This sample size also should allow for efficacy and safety analyses to be conducted within important subgroups such as sex, ethnicity, and baseline BMI.

3. Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.

- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

b. Secondary efficacy endpoints

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

In clinical practice, waist circumference is used as an indirect measure of visceral fat content, which when increased is associated with an elevated risk for metabolic abnormalities such as dyslipidemia and diabetes. Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that

reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters.

It is likely that a large portion of study subjects will be taking concomitant medications to treat weight-related comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Since weight loss is expected to improve these comorbidities, an important secondary efficacy endpoint should be the proportion of subjects treated with the weight-management product compared with placebo who have a meaningful dose-reduction or complete withdrawal of their concomitant medication. Algorithms that direct dose reduction or withdrawal of concomitant medications based on changes in levels of blood pressure, lipids, or glycemia should be included in the study protocols.

Measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints.

c. Efficacy benchmarks

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant

- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidites should be factored into the efficacy assessment of investigational weight-management products.

4. Standard of Care and Concomitant Medication

Overweight and obese patients enrolled in clinical studies of investigational weight-management products should receive standard of care, including medication, for comorbidities such as hypertension, dyslipidemia, and glycemic control.

5. Patients with Type 2 Diabetes

Compared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia following weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, sponsors should consider examining the efficacy and safety of weight-management products in trials dedicated to patients

with type 2 diabetes. The following recommendations should be considered when designing such trials:

- In general, patients should have baseline HbA1c levels between 8 percent and 10 percent.
- Patients should be excluded if they have fasting glucose levels greater than 270 mg/dl.
- Protocols should include escape criteria for poor glycemic control.
- Protocols should include an algorithm for the lowering or elimination of oral hypoglycemia or insulin dose based on fasting glucose levels and/or HbA1c (for patients who lose clinically significant amounts of weight).
- Patient randomization should be stratified by baseline antidiabetic medication (e.g., metformin versus sulfonylurea versus a thiazolidinedione versus insulin) and baseline HbA1c level (e.g., less than or equal to 9 percent versus greater than 9 percent).
- Hypoglycemia safety should be monitored.[3]

C. General Safety Assessment of Weight-Management Products

To ensure that drug or biologic-induced weight loss is caused primarily by a reduction in fat content, not lean-body mass, a representative sample of study subjects should have a baseline and follow-up measurement of body composition by DEXA, or a suitable alternative.

In addition to routine safety monitoring, it may be appropriate for the development programs of some weight-management products to have specialized safety assessments. For example, products that directly interact with the 5HT receptor system, specifically the $5HT_2$ receptor subtypes, probably should include evaluation of risk for cardiac valvulopathy using serial echocardiography. The development plans for centrally acting weight-management products generally should include validated assessments of neuropsychiatric function.

Assessment of the immunogenic potential of therapeutic proteins should be performed over a period of at least 6 to 12 months. If adverse events characteristic of allergic or immunologic reactions are identified, the FDA may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of an application for registration or may be conducted after approval as a postmarketing commitment, based on the overall analysis of the product's risks and benefits. The appropriate timing of such studies can be discussed with the FDA at a pre-biologics license application meeting or other similar advice meeting.

For centrally acting weight-management products, sponsors should anticipate the need to conduct preclinical and clinical studies of abuse liability. Sponsors are encouraged to discuss the design of these studies with members of CDER's Controlled Substance Staff during the early phases of product development.

[3] Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

The need for and details of specific safety monitoring may change as new data emerge. Sponsors are encouraged to discuss their plans for specific safety monitoring with the division during the early stages of product development.

D. Weight-Management Products Used in Combination

Two or more products may be combined into a single fixed-dosed combination when each component makes a contribution to the claimed effect or effects (21 CFR 300.50).

Before initiating long-term clinical studies with fixed-dose combinations, sponsors should conduct the appropriate preclinical and pharmacokinetics studies. (See the guidances for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* and *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.)

We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.

Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials.

The efficacy of a product combination for weight management generally will be assessed using the same factors as those applied to a single product, as defined in section IV.B.3.

E. Weight-Management Products for Patients with Medication-Induced Weight Gain

A number of drugs, notably psychotropic and some anticonvulsant agents, are associated with moderate-to-marked weight gain (Baptista and Zarate et al. 2004; Pierre and Picard 2001). In addition to increasing the risk for adverse health outcomes, medication-induced weight gain may reduce compliance with the drug responsible for the increased body weight.

Before initiating long-term clinical studies in patients with medication-induced weight gain, sponsors should rule out clinically significant drug-drug interactions and perform appropriate preclinical toxicological studies of the subject products. For details, see the guidances for industry *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and*

Recommendations for Dosing and Labeling, and *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

Patients eligible for participation in trials examining the efficacy and safety of products for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5 percent within 6 months of starting a drug known to cause weight gain. Patients should have BMIs greater than or equal to 27 kg/m^2 with comorbidities or greater than or equal to 30 kg/m^2 with or without comorbidities at the time of screening.

Because most weight-management products act within the central nervous system (CNS) and many of the drugs commonly associated with moderate-to-marked weight gain are used to treat psychiatric or neurological disorders, unique issues of efficacy and safety may arise in studies of products used to treat medication-induced weight gain. For example, it would be important to demonstrate that the efficacy and safety of the medication causing the weight gain (e.g., atypical antipsychotic) was not adversely affected by a weight-management product with a CNS mechanism of action, and vice versa. These and similar issues should be taken into account when designing and determining the sample size of trials for the treatment of medication-induced weight gain.

The efficacy of a product for the treatment of medication-induced weight gain generally will be assessed using the same factors as those for weight management, as defined in section IV.B.3.

Serotonin syndrome, a potentially life-threatening condition characterized by akathisia, tremor, altered mental status, clonus, muscular hypertonicity, and hyperthermia (Boyer and Shannon 2005), has been observed in patients exposed to a single or two or more proserotonergic agents used in combination. Therefore, in general, weight-management products that act as agonists at serotonin receptors, particularly the $5\text{-}HT2_A$ subtype, should not be studied in combination with proserotonergic medications associated with weight gain.

Because of issues related to safety and possibly efficacy that are unique to the particular combinations of drugs studied, approval of a product for weight management in patients with medication-induced weight gain generally will be limited to the weight-inducing drug studied and will not apply to the drug class in which the compound is a member. For example, if a weight-management product is shown to be effective and reasonably safe in the treatment of clozapine-induced weight gain, the approved indication would be limited to clozapine-induced weight gain and would not necessarily apply to the entire class of atypical or second generation antipsychotics.

V. CLINICAL ASSESSMENT OF LONG-TERM WEIGHT-MANAGEMENT PRODUCTS IN PEDIATRIC PATIENTS[4]

Because the benefit of weight-management products should be carefully weighed against potential toxicity, particularly in the pediatric population, we anticipate that phase 3 data in adults generally will be available before a new product is studied in children.

To ensure that the most appropriate dose or doses are studied in phase 3 trials, an assessment of the pharmacokinetics of a weight-management product in pediatric patients may be appropriate before initiation of long-term clinical studies. Pharmacokinetics and dose-ranging studies generally should include patients with age- and sex-matched BMIs greater than or equal to the 95th percentile.

Trials examining the efficacy and safety of a weight-management product in pediatric patients should be randomized, double-blind, placebo-controlled, and 1 year in duration. We suggest that initial pediatric studies be limited to adolescents (i.e., 12 to 16 year olds). Eligible patients should have age- and sex-matched BMIs greater than or equal to the 95th percentile (see http://www.cdc.gov/growthcharts). Patients should have a documented history of failing to lose sufficient weight with lifestyle modification before enrollment into studies of a weight-management product.

We recommend that initial clinical studies include patients with one or more weight-related comorbidities such as type 2 diabetes, dyslipidemia, or hypertension. Once a satisfactory risk-benefit profile has been established in this high-risk group of patients, studies of lower risk patients can be considered. Effort should be made to recruit equal numbers of males and females and representative samples of patients from ethnic groups in which the prevalence of obesity is high.

The lifestyle modification program should continue following randomization to product or placebo and its importance emphasized at appropriate intervals throughout the trials.

Because linear growth should be taken into account when assessing changes in the body weight of children and adolescents, the primary efficacy parameter in weight-management trials of pediatric patients should be a function of the change in BMI (e.g., the mean percent change in BMI and the proportion of patients who lose greater than or equal to 5 percent of baseline BMI). Height measurements should be obtained from a wall-mounted stadiometer.

Since demonstration of adequate safety necessitates a larger sample size than demonstration of efficacy, we anticipate that the sample size of the long-term pediatric weight-management studies will be determined by considerations of the product's mechanism of action and safety profile in adults. Sponsors should discuss and justify their proposed sample size with the division before initiating the study.

[4] For details on preclinical and pharmacokinetic evaluations for pediatric product development, see the ICH guidances for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutics* and *E11 Clinical Investigation of Medicinal Products in the Pediatric Population.*

In addition to standard safety evaluations specific to growing children (e.g., assessing Tanner stage at baseline and endpoint), studies of centrally acting weight-management products in pediatric patients also should include validated assessments of neuropsychiatric function. Other specialized safety assessments may be appropriate depending on the product's mechanism of action and its safety profile in adults.

The efficacy assessment of a weight-management product in pediatric patients will take into account the product's effectiveness in overweight and obese adults as well as the magnitude of the difference in the mean and categorical (greater than or equal to 5 percent) changes in BMI from baseline to Year 1 in pediatric patients treated with active product versus placebo.

VI. STATISTICAL CONSIDERATIONS

A. Sample Size

The number of subjects in a placebo-controlled trial should be the maximum of sample sizes calculated based on the co-primary endpoints of categorical response defined as greater than or equal to 5 percent reduction in baseline body weight after 1 year, and change from baseline weight. Calculations should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes for the calculations should represent clinically meaningful differences.

B. Preventing Missing Data from Premature Subject Withdrawal

Historically, there have been high rates of premature subject withdrawal in long-term trials of weight-management products. To allow for a true intent-to-treat (ITT) analysis, we encourage sponsors to obtain body weight measurements in all subjects who prematurely withdraw from late-stage preapproval trials near the calendar date at which they were scheduled to complete the trial (Simons-Morton and Obarzanek et al. 2006). For example, a subject who withdraws from a 12-month study after 6 months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation.

C. Analysis Methods

Response rates should be compared between treatment groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers subjects who are treated, drop out, and do not have complete post-baseline data as treatment failures.

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should

consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point. Statistical models should incorporate as factors any variables used to stratify the randomization. As important as assessing statistical significance is estimating the size of the treatment effect. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

D. Graphical Methods

Graphical methods showing treatment effects over time for completers should be presented. Cumulative distribution plots can be useful for showing response rates for different definitions of response based on the percentage of subjects with a change value equal to or less than the value on the x-axis selected to define the positive response. Additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

VII. LABELING CONSIDERATIONS

Data on the changes in the major weight-related comorbidities are important in assessing the overall risk-benefit profile of a new weight-management product and can be included in the Clinical Studies section of the product's labeling. However, it is important to recognize that even though secondary efficacy endpoints are prespecified and the overall type 1 error rate is controlled for, that does not necessarily guarantee that all secondary endpoints will be included in labeling if the differences between active-product and placebo-treated groups are of nominal statistical significance. The clinical significance and consistency across studies of any observed differences will be important in determining whether the secondary efficacy data merit inclusion in the Clinical Studies section of the labeling.

VIII. STAND-ALONE INDICATIONS FOR THE PREVENTION OR TREATMENT OF WEIGHT-RELATED COMORBIDITIES

As mentioned earlier, weight loss through lifestyle modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidites are expected following drug or biologic-induced weight loss, and from a regulatory perspective, they are considered part of the weight-management indication. Thus, for a weight-management product to obtain a stand-alone indication for the prevention or treatment of type 2 diabetes, dyslipidemia, hypertension, or any other weight-related comorbidity, it should be shown that the product effectively prevents or treats the comorbidity through a mechanism that is independent of weight loss.

IX. METABOLIC SYNDROME

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. The FDA does not necessarily consider the metabolic syndrome to represent a distinct disease entity. At present, there is no single etiological factor or central pathogenetic abnormality identified as mediating the constellation of excess visceral adiposity, abnormal lipids, elevated blood pressure, and insulin resistance that comprise the metabolic syndrome. Nonetheless, in addition to lifestyle modification, a host of drug therapies now exist to address individual or multiple components of the syndrome (e.g., lipid altering agents, antihypertensives, insulin sensitizers). Ideally, a therapeutic product intended to treat metabolic syndrome should *normalize* or improve all components of the syndrome, independent of weight loss (see section VIII), and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality.

REFERENCES

American Academy of Pediatrics, 2003, Policy Statement, Committee on Nutrition. Prevention of Pediatric Overweight and Obesity, *Pediatrics*, 112:424-430.

Baptista, T, J Zarate, R Joober, C Colasante, S Beaulieu et al., 2004, Drug-Induced Weight Gain, An Impediment to Successful Pharmacotherapy: Focus on Antipsychotics, *Current Drug Targets*, 5:279-299.

Barlow, SE and WH Dietz, 1998, Obesity Evaluation and Treatment: Expert Committee Recommendations, *Pediatrics*, 102(3):e29.

Boyer, EW and M Shannon, 2005, The Serotonin Syndrome, *New England Journal of Medicine*, 352:1112-1120.

Calle, EE, MJ Thun, JM Petrelli, C Rodriquez, and CW Heath, 1999, Body Mass Index and Mortality in a Prospective Cohort of U.S. Adults, *New England Journal of Medicine*, 341:1097-1105.

Caterson, ID, V Hubbard, GA Bray, R Grunstein, BC Hansen et al., 2004, Obesity, A Worldwide Epidemic Related to Heart Disease and Stoke, *Circulation*, 110:e476-e483.

Cheymol, G, 2000, Effects of Obesity on Pharmacokinetics — Implications for Drug Therapy, *Clinical Pharmacokinetics*, 39:215-231.

Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults, The Evidence Report, 1998, NIH Publication No. 98-4083.

Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

Dietz, WH and TN Robinson, 2005, Overweight Children and Adolescents, *New England Journal of Medicine*, 352(20):2100-2109.

Douketis, JD, C Macie, L Thabane, and DF Williamson, 2005, Systematic Review of Long-Term Weight Loss Studies in Obese Adults: Clinical Significance and Applicability to Clinical Practice, *International Journal of Obesity*, 29:1153-1167.

Eilat-Adar, S, M Eldar, and U Goldbourt, 2004, Association of Intentional Changes in Body Weight with Coronary Heart Disease Event Rates in Overweight Subjects Who Have an Additional Coronary Risk Factor, *American Journal of Epidemiology*, 161:352-358.

Gregg, EW, RB Gerzoff, TJ Thompson, and DF Williamson, 2003, Intentional Weight Loss and Death in Overweight and Obese U.S. Adults 35 Years of Age and Older, *Annals of Internal Medicine*, 138:383-389.

Janssen, I, PT Katzmarzyk, and R Ross, 2004, Waist Circumference and not Body Mass Index Explains Obesity-Related Health Risk, *American Journal of Clinical Nutrition*, 79:379-384.

Parker, ED and AR Folsom, 2003, Intentional Weight Loss and Incidence of Obesity-Related Cancers: The Iowa Women's Health Study, *International Journal of Obesity*, 27:1447-1452.

Pierre, J and F Picard, 2001, Bodyweight Gain and Anticonvulsants, A Comparative Review, *Drug Safety*, 24:969-978.

Pi-Sunyer, FX, 2004, The Epidemiology of Central Fat Distribution in Relation to Disease, *Nutrition Reviews*, 62:S120-126.

The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 2000, NIH Publication No. 00-4084.

Rexrode, KM, VJ Carey, CH Hennekens, EE Walters, GA Colditz et al., 1998, Abdominal Obesity and Coronary Heart Disease in Women, *Journal of the American Medical Association*, 280:1843-1848.

Simons-Morton, D, E Obarzanek, and J Cutler, 2006, Obesity Research-Limitations of Methods, Measurements, and Medications, *Journal of the American Medical Association*, 295:826-828.

Speiser, P, M Rudolf, H Anhalt, C Camacho-Hubner, F Chiarelli et al., 2005, Childhood Obesity, *The Journal of Clinical Endocrinology & Metabolism*, 90(3):1871-1887.

Zhu, S, Z Wang, S Heshka, M Heo, MS Faith et al., 2002, Waist Circumference and Obesity-Associated Risk Factors Among Whites in the Third National Health and Nutrition Examination Survey: Clinical Action Thresholds, *American Journal of Clinical Nutrition*, 76:743-749.

12.3 Appendix 3: Clinical Program Summary Tables

Table 43. Summary of Phase 3 Clinical Studies: Design and Key Results

Study No. (No. of Centers)	Study Design	Treatments	No. and Type of Subjects Randomized (Completed)	Key Efficacy Results – ITT Set	Key Safety Results
OB-301 (34 in US)	Randomized, double-blind, placebo-controlled, parallel	• Placebo • Phentermine 7.5 mg • Topriamate 46 mg • QNEXA (PHEN/TPM) 7.5/46 mg • Phentermine 15 mg • Topiratmate 92 mg • QNEXA (PHEN/TPM) 15/92 mg	Adult subjects with BMI ≥30 kg/m^2 and ≤45 kg/m^2 756 (541)	**Percent Weight Loss at Week 28 With LOCF:** **Treatment** / **LS Mean (SE)** / **p-value [1]** Placebo 1.7 (0.61) – PHEN 7.5 5.5 (0.61) – TPM 46 5.1 (0.61) – PHEN/TPM 7.5/46 8.5 (0.62) <0.0001 PHEN 15 6.1 (0.61) – TPM 92 6.4 (0.62) – PHEN/TPM 15/92 9.2 (0.61) <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 28 With LOCF:** **Treatment** / **n (%)** / **p-value [1]** Placebo 16 (15.5) – PHEN 7.5 45 (43.3) – TPM 46 40 (39.2) – PHEN/TPM 7.5/46 64 (62.1) <0.0001 PHEN 15 49 (46.2) – TPM 92 51 (48.6) – PHEN/TPM 15/92 68 (66.0) <0.0001	**Subjects With SAEs:** **Treatment** / **n (%)** Placebo 0 (0.0) PHEN 7.5 2 (1.8) TPM 46 0 (0.0) PHEN/TPM 7.5/46 1 (0.9) PHEN 15 1 (0.9) TPM 92 1 (0.9) PHEN/TPM 15/92 2 (1.9) **Study Drug Discontinuations due to Adverse Events:** **Treatment** / **n (%)** Placebo 8 (7.3) PHEN 7.5 10 (9.2) TPM 46 8 (7.5) PHEN/TPM 7.5/46 16 (15.1) PHEN 15 11 (10.2) TPM 92 18 (16.8) PHEN/TPM 15/92 23 (21.3)

Study No. (No. of Centers)	Study Design	Treatments	No. and Type of Subjects Randomized (Completed)	Key Efficacy Results – ITT Set	Key Safety Results
OB-302 (91 in US)	Randomized, double-blind, placebo-controlled, parallel	• Placebo • QNEXA (PHEN/TPM) 3.75/23 mg • QNEXA (PHEN/TPM) 15/92 mg	Adult subjects with BMI ≥35 kg/m^2 1267 (759)	**Percent Weight Loss at Week 56 With LOCF:** **Treatment / LS Mean (SE) / p-value [1]** Placebo 1.6 (0.40) – PHEN/TPM 3.75/23 5.1 (0.54) <0.0001 PHEN/TPM 15/92 10.9 (0.39) <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 56 With LOCF:** **Treatment / n (%) / p-value [1]** Placebo 86 (17.3) – PHEN/TPM 3.75/23 105 (44.9) <0.0001 PHEN/TPM 15/92 332 (66.7) <0.0001	**Subjects With SAEs:** **Treatment / n (%)** Placebo 13 (2.5) PHEN/TPM 3.75/23 6 (2.5) PHEN/TPM 15/92 13 (2.5) **Study Drug Discontinuations due to Adverse Events:** **Treatment / N (%)** Placebo 43 (8.4) PHEN/TPM 3.75/23 28 (11.7) PHEN/TPM 15/92 83 (16.2)
OB-303 (93 in US)	Randomized, double-blind, placebo-controlled, parallel	• Placebo • QNEXA (PHEN/TPM) 7.5/46 mg • QNEXA (PHEN/TPM) 15/92 mg	Adult subjects with BMI ≥27 kg/m^2 and ≤45 kg/m^2 with weight-related co-morbidities 2487 (1723)	**Percent Weight Loss at Week 56 With LOCF:** **Treatment / LS Mean (SE) / p-value [1]** Placebo 1.2 (0.28) – PHEN/TPM 7.5/46 7.8 (0.37) <0.0001 PHEN/TPM 15/92 9.8 (0.28) <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 56 With LOCF:** **Treatment / n (%) / p-value [1]** Placebo 204 (20.8) – PHEN/TPM 7.5/46 303 (62.1) <0.0001 PHEN/TPM 15/92 687 (70.0) <0.0001	**Subjects With SAEs:** **Treatment / n (%)** Placebo 40 (4.0) PHEN/TPM 7.5/46 15 (3.0) PHEN/TPM 15/92 50 (5.0) **Study Drug Discontinuations due to Adverse Events:** **Treatment / n (%)** Placebo 89 (9.0) PHEN/TPM 7.5/46 58 (11.6) PHEN/TPM 15/92 192 (19.3)

1. Two-sided p-value from treatment comparison of QNEXA (PHEN/TPM) with placebo.

BMI=body mass index; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; PHEN=VIVUS's immediate-release phentermine hydrochloride beads; QNEXA=VIVUS's fixed-dose combination of PHEN and TPM; SAE=serious adverse event; SE=standard error; TPM=VIVUS's modified-release topiramate beads.

Table 44. Summary of Phase 2 Clinical Studies: Design and Key Results

Study No. (No. of Centers)	Study Design	Treatments	No. and Type of Subjects Randomized (Completed)	Key Efficacy Results – ITT Set	Key Safety Results
OB-201 (1 in US)	Randomized, double-blind, placebo-controlled, parallel	• Placebo • Phentermine 15 mg • Topiramate 100 mg • Phentermine 15 mg and topiramate 100 mg	Adult subjects with BMI ≥30 kg/m^2 and ≤50 kg/m^2 200 (158)	**Percent Weight Loss at Week 24 With LOCF:** **Treatment** / **LS Mean (SE)** / **p-value [1]** Placebo: 2.1 (0.82) / – Phentermine 15: 4.6 (0.82) / – Topiramate 100: 6.3 (0.81) / – Phentermine 15 and topiramate 100: 10.7 (0.82) / <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 24 With LOCF:** **Treatment** / **n (%)** / **p-value [2]** Placebo: 7 (14.0) / – Phentermine 15: 19 (38.0) / – Topiramate 100: 25 (50.0) / – Phentermine 15 and topiramate 100: 41 (82.0) / <0.0001	**Subjects With SAEs:** **Treatment** / **n (%)** Placebo: 0 (0.0) Phentermine 15: 0 (0.0) Topiramate 100: 0 (0.0) Phentermine 15 and topiramate 100: 0 (0.0) **Study Discontinuations due to Adverse Events:** **Treatment** / **n (%)** Placebo: 3 (6.0) Phentermine 15: 3 (6.0) Topiramate 100: 3 (6.0) Phentermine 15 and topiramate 100: 1 (2.0)
OB-202 (10 in US)	Randomized, double-blind, placebo-controlled, parallel	• Placebo • Phentermine 15 mg and topiramate 100 mg	Adult subjects with BMI ≥27 kg/m^2 and ≤45 kg/m^2 with type 2 diabetes 210 (165)	**Percent Weight Loss at Week 28 with LOCF:** **Treatment** / **LS Mean (SE)** / **p-value [3]** Placebo: 1.2 (0.56) Phentermine 15 and topiramate 100: 8.0 (0.57) / <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 28 With LOCF:** **Treatment** / **n (%)** / **p-value [4]** Placebo: 14 (14) Phentermine 15 and topiramate 100: 60 (61) / <0.0001 **Change in HbA_{1c} (%) at Week 28 With LOCF:** **Treatment** / **LS Mean (SE)** / **p-value [3]** Placebo: -0.6 (0.11) Phentermine 15 and topiramate 100: -1.1 (0.12) / 0.0007	**Subjects With SAEs:** **Treatment** / **n (%)** Placebo: 4 (3.8) Phentermine 15 and topiramate 100: 4 (3.9) **Study Discontinuations due to Adverse Events:** **Treatment** / **n (%)** Placebo: 4 (3.8) Phentermine 15 and topiramate 100: 3 (2.9)

Study No. (No. of Centers)	Study Design	Treatments	No. and Type of Subjects Randomized (Completed)	Key Efficacy Results – ITT Set	Key Safety Results
DM-230 (10 in US)	Randomized, double-blind, placebo-controlled, parallel, extension of OB-202	• Placebo • QNEXA (PHEN/TPM) 15/92 mg	Adult subjects who completed study OB-202 (BMI ≥27 kg/m^2 and ≤45 kg/m^2 with type 2 diabetes) 130 (120)	**Percent Weight Loss at Week 56 With LOCF [5]:** **Treatment** / **LS Mean (SE)** / **p-value [3]** Placebo: 2.7 (0.95) PHEN/TPM 15/92: 9.4 (0.81); <0.0001 **Number (%) of Subjects With ≥5% Weight Loss at Week 56 With LOCF [5]:** **Treatment** / **n (%)** / **p-value [4]** Placebo: 13 (24) PHEN/TPM 15/92: 49 (65); <0.0001 **Change in HbA_{1c} (%) at Week 56 With LOCF [5]:** **Treatment** / **LS Mean (SE)** / **p-value [3]** Placebo: -1.2 (0.13) PHEN/TPM 15/92: -1.6 (0.11); 0.0381	**Subjects With SAEs:** **Treatment** / **n (%)** Placebo: 1 (1.8) PHEN/TPM 15/92: 2 (2.7) **Study Discontinuations due to Adverse Events:** **Treatment** / **n (%)** Placebo: 0 (0.0) PHEN/TPM 15/92: 1 (1.3)
DM-231 (9 in US)	Open-label, uncontrolled extension of DM-230 (terminated early after 16 weeks of treatment)	• QNEXA (PHEN/TPM) 15/92 mg	Adult subjects who completed study DM-230 (BMI ≥27 kg/m^2 and ≤45 kg/m^2 with type 2 diabetes) 101 (0)	**Percent Weight Loss at Week 72 [5]:** **Treatment** / **Mean (SD)** PHEN/TPM 15/92 16-week population: 8.4 (6.78) 72-week population: 10.1 (8.74) **Number (%) of Subjects With ≥5% Weight Loss at Week 72 [5]:** **Treatment** / **n (%)** PHEN/TPM 15/92 16-week population: 31 (70.5) 72-week population: 40 (70.2) **Change in HbA_{1c} (%) at week 72 [5]:** **Treatment** / **Mean (SD)** PHEN/TPM 15/92 16-week population: -1.7 (1.10) 72-week population: -1.4 (1.34)	**Subjects With SAEs:** **Treatment** / **n (%)** PHEN/TPM 15/92: 1 (1.0) **Study Discontinuations due to Adverse Events:** **Treatment** / **n (%)** PHEN/TPM 15/92: 3 (3.0)

Study No. (No. of Centers)	Study Design	Treatments	No. and Type of Subjects Randomized (Completed)	Key Efficacy Results – ITT Set	Key Safety Results
OB-205 (1 in US)	Randomized, double-blind, placebo-controlled, crossover	• Placebo • QNEXA (PHEN/TPM) 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15/92 mg)	Adult subjects with BMI ≥27 kg/m^2 and ≤35 kg/m^2 80 (36)	NA	**Subjects With SAEs:** **Treatment** **n (%)** Placebo 0 (0.0) PHEN/TPM 0 (0.0) **Study Discontinuations due to Adverse Events:** **Treatment** **n (%)** Placebo 0 (0.0) PHEN/TPM 1 (2.6)

1. p-values for comparing treatments were obtained from an ANCOVA model with fixed effects for treatment and sex and baseline weight and baseline BMI as covariates.
2. p-values determined by Fisher's exact test.
3. p-value for comparing treatments was obtained using an ANCOVA model with treatment as a fixed effect and baseline weight as a covariate.
4. p-value for comparing treatments was obtained using a logistic regression model with terms for treatment and baseline weight as a covariate.
5. Baseline values for studies DM-230 and DM-231 were obtained at Week 0 of study OB-202.

ANCOVA=analysis of covariance; BMI=body mass index; HbA_{1c}=hemoglobin A_{1c}; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; PHEN=VIVUS's immediate-release phentermine hydrochloride beads; QNEXA=VIVUS's fixed-dose combination of PHEN and TPM; SAE=serious adverse event; SD=standard deviations; SE=standard error; TPM=VIVUS's modified-release topiramate beads.

Table 45. Summary of Phase 1 Clinical Pharmacology Studies: Design and Key Safety Results

Study No. (No. of Centers)	Study Design	Treatments/Regimens	No. and Type of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean Age	Sex	Race	
OB-101 (1 in US)	Randomized, open-label, crossover (single-dose pharmacokinetics)	A: Phentermine 15 mg and topiramate 25 mg (co-administered doses) B: Phentermine 15 mg and topiramate 100 mg (co-administered doses) C: Phentermine 15 mg and topiramate 125 mg (co-administered doses) D: Phentermine 15 mg and topiramate 100 mg (split doses)	Adult subjects with BMI ≥27 kg/m^2 and ≤42 kg/m^2 16 (15)	35 years	50% F 50% M	50% C 31% AA 13% A 6% O	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 1
OB-102 (1 in US)	Randomized, open-label, parallel (single- and multiple-dose pharmacokinetics)	A: Phentermine 7.5 mg and topiramate 50 mg (co-administered doses) B: Phentermine 15 mg and topiramate 100 mg (co-administered doses) C: Phentermine 15 mg and topiramate 100 mg (co-administered doses)	Adult subjects with BMI ≥30 kg/m^2 and ≤42 kg/m^2 45 (39)	37 years	53% F 47% M	82% C 7% AA 11% O	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0
OB-103 (1 in US)	Randomized, open-label, parallel (single dose, food effect, drug interaction between phentermine and topiramate)	A: QNEXA (PHEN/TPM) 15/92 mg (fasted) B: QNEXA (PHEN/TPM) 15/92 mg (fed) C: Phentermine 15 mg (fasted) D: Topiramate 92 mg (fasted)	Adult subjects with BMI ≥30 kg/m^2 and ≤45 kg/m^2 65 (65)	36 years	49% F 51% M	88% C 8% AA 2% A 3% O	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0

Study No. (No. of Centers)	Study Design	Treatments/Regimens	No. and Type of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean Age	Sex	Race	
OB-105 (2 in US)	Open-label, parallel (single-dose pharmacokinetics in subjects with normal hepatic function and with subjects with hepatic impairment)	QNEXA (PHEN/TPM) 15/92 mg	Adult subjects with BMI ≥21 kg/m^2 and ≤38 kg/m^2 with mild to moderate hepatic impairment (healthy control subjects) 24 (24)	53 years	25% F 75% M	92% C 8% AA	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0
OB-106 (4 in US)	Open-label, parallel (single-dose pharmacokinetics in subjects with normal renal function and subjects with renal impairment)	QNEXA (PHEN/TPM) 15/92 mg	Adult subjects with BMI ≥18 kg/m^2 and ≤40 kg/m^2 with mild to severe renal impairment (healthy control subjects) 33 (32)	68 years	73% F 27% M	82% C 15% AA 3% O	Subjects with SAEs, n: 1 Discontinuations due to AEs, n: 1
OB-107 (1 in US)	Open-label, fixed-sequence crossover (drug-drug interaction)	Treatment sequence: Metformin 500 mg BID Sitagliptin 100 mg QD QNEXA (PHEN/TPM) 15/92 mg QD QNEXA + probenecid 2 g QNEXA + metformin QNEXA + sitagliptin	Healthy adult subjects with BMI ≥19 kg/m^2 and ≤35 kg/m^2 20 (19)	35 years	50% F 50% M	100% C	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0
OB-108 (1 in US)	Open-label, fixed-sequence (drug-drug interaction)	Treatment sequence: Norethindrone 1.0 mg and ethinyl estradiol 0.03 mg QNEXA (PHEN/TPM) 15/92 mg (titration sequence)	Adult female subjects with BMI ≥27 kg/m^2 and ≤35 kg/m^2 20 (20)	33 years	100% F	95% C 5% AA	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0

Study No. (No. of Centers)	Study Design	Treatments/Regimens	No. and Type of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean Age	Sex	Race	
OB-109 (1 in US)	Randomized, open-label, parallel (single-dose bioequivalence)	A: QNEXA (PHEN/TPM) 3.75/23 mg (no sugar sphere filler) B: QNEXA (PHEN/TPM) 3.75/23 mg (sugar sphere filler) C: QNEXA (PHEN/TPM) 7.5/46 mg (no sugar sphere filler) D: QNEXA (PHEN/TPM) 7.5/46 mg (sugar sphere filler) E: QNEXA (PHEN/TPM) 11.25/69 mg (no sugar sphere filler) F: QNEXA (PHEN/TPM) 11.25/69 mg (sugar sphere filler)	Adult subjects with BMI ≥30 kg/m^2 and ≤42 kg/m^2 230 (229)	36 years	48% F 52% M	96% C 3% AA 1% O	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0
OB-110 (1 in US)	Randomized, open-label, parallel (single-dose bioavailability)	A: QNEXA (PHEN/TPM) 15/92 mg B: Phentermine 37.5 mg C: Topiramate 100 mg	Adult subjects with BMI ≥30 kg/m^2 and ≤42 kg/m^2 41 (41)	35 years	51% F 49% M	98% C 2% O	Subjects with SAEs, n: 0 Discontinuations due to AEs, n: 0
OB-118 (1 in US)	Randomized, double-blind, placebo- and active-controlled, parallel/crossover (QT/QTc)	A: Placebo B: Moxifloxacin C: QNEXA (PHEN/TPM) (3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15/92 mg, 22.5/138 mg)	Adult subjects with BMI ≥24 kg/m^2 and ≤30 kg/m^2 112 (108)	33 years	50% F 50% M	97% C 3% AA	Subjects with SAEs, n: 1 Discontinuations due to AEs, n: 2

A=Asian; AE=adverse event; AA=African American; BID=twice daily; BMI=body mass index; C=Caucasian; F=female; M=male; O=Other; PHEN=VIVUS's immediate-release phentermine hydrochloride beads; QD=once daily; QNEXA=VIVUS's fixed-dose combination of PHEN and TPM; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; QTc=QT interval corrected for heart rate; SAE=serious adverse event; TPM=VIVUS's modified-release topiramate beads.

12.4 Appendix 4: Assessment Tools

12.4.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime For Baseline or Since Last Assessment**	**Last Week**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you tried to harm yourself in order to end your life or because you wanted to die/kill yourself?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from…?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) **Indicate if subject has engaged in Non-Suicidal Self-Injurious Behavior :**	**Yes No** ☐ ☐ Total # of attempts _____	**Yes No** ☐ ☐ Total # of attempts _____
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.	**Yes No** ☐ ☐ Total # of aborted	**Yes No** ☐ ☐ Total # of aborted

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime For Baseline or Since Last Assessment**	**Last Week**
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?	____	____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Absence of Suicidal Behavior: No suicidal behavior present during the assessment period.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

SUICIDAL IDEATION		
Ask about all 5 types of ideation, starting with least severe (wish to be dead) through most severe.	**Since Last Assessment or For Baseline Time He/She Felt Most Suicidal**	**Last Week**
Non-suicidal Suicidal ideation present during the assessment period.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
1. Wish to be Dead Subject endorses thoughts about their own death, including any of the following: a wish to be dead/better off dead, wish he/she were never born, thoughts that life is not worth living or the world would be better off without him/her, wish to fall asleep and not wake up, ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Do you think that it might be better if you weren't alive any more?*** ***Frequency of Ideation:*** _____	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide *"I've thought about killing myself"* without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?***	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

SUICIDAL IDEATION		
Frequency of Ideation: _____		
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** ***Frequency of Ideation:*** _____	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation:*** _____	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation:*** _____	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

12.4.2 Impact of Weight on Quality of Life Questionnaire - Lite Version (IWQOL-Lite©)

List of Questions

Physical Function
1. Because of my weight I have trouble picking up objects.
2. Because of my weight I have trouble tying my shoes.
3. Because of my weight I have difficulty getting up from chairs.
4. Because of my weight I have trouble using stairs.
5. Because of my weight I have difficulty putting on or taking off my clothing.
6. Because of my weight I have trouble with mobility.
7. Because of my weight I have trouble crossing my legs.
8. I feel short of breath with only mild exertion.
9. I am troubled by painful or stiff joints.
10. My ankles and lower legs are swollen at the end of the day
11. I am worried about my health.

Self-Esteem
1. Because of my weight I am self-conscious.
2. Because of my weight my self-esteem is not what it could be.
3. Because of my weight I feel unsure of myself.
4. Because of my weight I don't like myself.
5. Because of my weight I am afraid of being rejected.
6. Because of my weight I avoid looking in mirrors or seeing myself in photographs.
7. Because of my weight I am embarrassed to be seen in public places.

Sexual Life
1. Because of my weight I do not enjoy sexual activity.
2. Because of my weight I have little or no sexual desire.
3. Because of my weight I have difficulty with sexual performance.
4. Because of my weight I avoid sexual encounters whenever possible.

Public Distress
1. Because of my weight I experience ridicule, teasing, or unwanted attention.
2. Because of my weight I worry about fitting into seats in public places (e.g., theaters, restaurants, cars, or airplanes).
3. Because of my weight I worry about fitting through aisles or turnstiles.
4. Because of my weight I worry about finding chairs that are strong enough to hold my weight.
5. Because of my weight I experience discrimination by others.

Work
1. Because of my weight I have trouble getting things accomplished or meeting my responsibilities.
2. Because of my weight I am less productive than I could be.
3. Because of my weight I don't receive appropriate raises, promotions or recognition at work.

4. Because of my weight I am afraid to go on job interviews.

[1] Questionnaire Results: 1 = Never True, 2 = Rarely True, 3 = Sometimes True, 4 = Usually True, 5 = Always True.
[2] For raw scores, a lower score indicates a higher quality of life. For transformed scores, a higher score indicates a higher quality of life.

12.4.3 Patient Health Questionnaire (PHQ-9) for Depression

PATIENT HEALTH QUESTIONNAIRE PHQ-9 FOR DEPRESSION

USING PHQ-9 DIAGNOSIS AND SCORE FOR INITIAL TREATMENT SELECTION

A depression diagnosis that warrants treatment or treatment change, needs at least one of the first two questions endorsed as positive (*little pleasure, feeling depressed*) indicating the symptom has been present more than half the time in the past two weeks.

In addition, the tenth question about difficulty at work or home or getting along with others should be answered at least "somewhat difficult."

When a depression diagnosis has been made, patient preferences should be considered, especially when choosing between treatment recommendations of antidepressant treatment and psychotherapy.

PHQ-9 Score	Provisional Diagnosis	Treatment Recommendation
5-9	Minimal symptoms*	Support, educate to call if worse; return in 1 month.
10-14	Minor depression ††	Support, watchful waiting
	Dysthymia*	Antidepressant or psychotherapy
	Major depression, *mild*	Antidepressant or psychotherapy
15-19	Major depression, *moderately severe*	Antidepressant or psychotherapy
≥ 20	Major depression, *severe*	Antidepressant and psychotherapy (especially if not improved on monotherapy)

* If symptoms present ≥ two years, then probable chronic depression which warrants antidepressant or psychotherapy (ask, *"In the past 2 years have you felt depressed or sad most days, even if you felt okay sometimes?"*).

†† If symptoms present ≥ one month or severe functional impairment, consider active treatment.

USING THE PHQ-9 TO ASSESS PATIENT RESPONSE TO TREATMENT

- The goal of acute phase treatment is remission of symptoms as indicated by a PHQ-9 Score of < 5 points.
- Patients who achieve this goal enter into the continuation phase of treatment.
- Patients who do not achieve this goal remain in acute phase treatment and require some alteration in treatment (dose increase, augmentation, combination treatment).
- Patients who do not achieve remission after two adequate trials of antidepressant and/or psychological counseling or by 20 to 30 weeks would benefit from a formal or informal psychiatric consultation for diagnostic and management suggestions.

Initial Response after Four - Six weeks of an Adequate Dose of an Antidepressant		
PHQ-9 Score	**Treatment Response**	**Treatment Plan**
Drop of ≥ 5 points from baseline	Adequate	No treatment change needed. Follow-up in four weeks.
Drop of 2-4 points from baseline.	Probably Inadequate	Often warrants an increase in antidepressant dose
Drop of 1-point or no change or increase.	Inadequate	Increase dose; Augmentation; Switch; Informal or formal psychiatric consultation; Add psychological counseling
Initial Response to Psychological Counseling after Three Sessions over Four - Six weeks		
PHQ-9 Score	**Treatment Response**	**Treatment Plan**
Drop of ≥ 5 points from baseline	Adequate	No treatment change needed. Follow-up in four weeks.
Drop of 2-4 points from baseline.	Probably Inadequate	Possibly no treatment change needed. Share PHQ-9 with psychological counselor.
Drop of 1-point or no change or increase.	Inadequate	If depression-specific psychological counseling (CBT, PST, IPT*) discuss with therapist, consider adding antidepressant. For patients satisfied in other type of psychological counseling, consider starting antidepressant For patients dissatisfied in other psychological counseling, review treatment options and preferences

** CBT – Cognitive-Behavioral Therapy; PST – Problem Solving Treatment; IPT – Interpersonal Therapy*

Use of the PHQ-9 to Make a Tentative Depression Diagnosis
(Symptomatology & Functional Impairment)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

STEP 1:
Need one or both questions endorsed as "2" or "3" ("More than half the days" or "Nearly every day")

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3			1	2	3
4			1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yo		1	2	3

STEP 2:
Need a total of five or more boxes endorsed within the shaded areas of the form to arrive at the total SYMPTOM COUNT.

STEP 3:
FUNCTIONAL IMPAIRMENT is endorsed as "somewhat difficult" or greater.

TOTAL SYMPTOMS endorsed more than half the days
(except question 9 - any positive endorsement)

10	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all Somewhat difficult Very difficult Extremely difficult

Use of the PHQ-9 for Treatment Selection & Monitoring
(Determining a Severity Score)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
			1	2	3
			1	2	3
			1	2	3
			1	2	3
8	Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
	STEP 4: Add the totals for each of the three columns together. Enter the TOTAL. This is the SEVERITY SCORE.	umns:			
		OTAL:			
10	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all Somewhat difficult Very difficult Extremely difficult			

STEP 1:
Count each item in the column labeled "Several Days" and multiply by one. Enter that number below that column.
STEP 2:
Count each item in the column labeled "More than half the days" and multiply by two. Enter that number below that column.
STEP 3:
Count each item in the column labeled "Nearly every day" and multiply by three. Enter that number below that column.
STEP 4:
Add the totals for each of the three columns together. This is the SEVERITY SCORE.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ **DATE:** _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
	add columns:		+	+
	TOTAL:			

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	**Not difficult at all** _____ **Somewhat difficult** _____ **Very difficult** _____ **Extremely difficult** _____

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Spitzer at rls8@columbia.edu. Use of the PHQ-9 may only be made in accordance with the Terms of Use available at *http://www.pfizer.com*. PRIME MD TODAY is a trademark of Pfizer Inc.

12.4.4 SF-36 Questionnaire

SF-36 QUESTIONNAIRE

Name:_____ Ref. Dr:_____ Date: _____

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?
○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bathing or dressing yourself
○Yes, Limited a Lot ○Yes, Limited a Little ○No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Were limited in the kind of work or other activities
○Yes ○No

Had difficulty performing the work or other activities (for example, it took extra effort)
○Yes ○No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Didn't do work or other activities as carefully as usual
○Yes ○No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

○Not at all ○Slightly ○Moderately ○Severe ○Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

○None ○Very Mild ○Mild ○Moderate ○Severe ○Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

○Not at all ○A little bit ○Moderately ○Quite a bit ○Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Did you feel worn out?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you been a happy person?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Did you feel tired?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ All of the time
- ○ Most of the time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I am as healthy as anybody I know
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I expect my health to get worse
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

My health is excellent
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

12.5 Appendix 5: Overview of Biopharmaceutics

In early proof-of-concept studies evaluating the combined use of phentermine hydrochloride and topiramate, immediate-release phentermine was administered in the morning and immediate-release topiramate was administered in the evening, so that the peak exposures to each drug would occur at a time of day that would minimize the impact of each drug's side effects. The QNEXA formulation was designed to mimic this sequence of exposure, using a single capsule administered in the morning. The PHEN beads in QNEXA provide immediate release of phentermine, allowing peak exposure to occur in the morning with a morning dose of QNEXA. The TPM beads in QNEXA are formulated for delayed release of topiramate, which lowers the maximum observed plasma drug concentration (C_{max}) and delays the time to maximum plasma concentration (T_{max}). The delay in T_{max} with TPM relative to immediate-release topiramate allows peak topiramate exposure to occur in the evening with a morning dose of QNEXA. This target pharmacokinetic (PK) profile leads to optimal coverage to sustain efficacy, mitigate potential side effects, and minimize drug-drug interaction between phentermine and topiramate. Overall, this PK profile may contribute to improved patient compliance and tolerability of QNEXA compared to combination therapy with immediate-release formulations of phentermine and topiramate.

The QNEXA capsules used in most of the clinical studies for QNEXA were identical in formulation, composition, and method of manufacture to those proposed for commercial use. Apart from the number of PHEN and TPM beads loaded into capsules, the formulations across all doses of QNEXA were identical. In study OB-102, the beads were manufactured at laboratory scale; however, the composition and formulation were identical to those proposed for commercial use. In study OB-101C, only marketed phentermine HCl and topiramate drug products were used. During clinical development, capsules of QNEXA Low dose, QNEXA Mid dose, and QNEXA Three-Quarter dose included blank sugar spheres (Formulation A) to blind the study by closely matching the total fill volume of the QNEXA Top-dose capsules. For the proposed commercial product, no sugar sphere filler will be added to capsules (Formulation B). In a bioequivalence study, Formulation B was found to be bioequivalent to Formulation A for QNEXA Low dose, QNEXA Mid dose, and QNEXA Three-Quarter dose. Since the QNEXA

Top dose capsules used in the clinical studies were identical in formulation and method of manufacture to the proposed commercial formulation, a bioequivalence study for the QNEXA Top dose capsule was not required.

The co-administration of a high-fat meal with QNEXA had no effect on the PK of phentermine and topiramate. Therefore, QNEXA may be administered with food.

The phentermine exposure from one QNEXA Top dose capsule did not exceed the exposure from one Adipex-P® 37.5 mg tablet. The topiramate exposure from one QNEXA Top dose capsule did not exceed the exposure from one Topamax® 100 mg tablet.

The phentermine and topiramate exposure from the concomitant administration of single or multiple doses of QNEXA (PHEN 15 mg capsules and TPM 100 mg capsules) did not exceed the exposure from the concomitant administration of Adipex-P 15 mg tablets and Topamax 100 mg tablets.

12.6 Appendix 6: MACE Events

OB-302 / Subject 116-036 – QNEXA Low dose
MACE: Myocardial infarction

A 62-year-old obese (body mass index [BMI] 37.5 kg/m^2) Caucasian female experienced a myocardial infarction approximately 2 months after being randomized to QNEXA in OB-302. Her relevant current medical conditions included coronary artery disease, hypertension, dyslipidemia, and heart murmur. Her past medical history included cigarette smoking, which she quit in 1968. She was not taking any relevant concomitant medications at the time of the event.

The subject was randomized to QNEXA Low dose on 19 Jan 2008. She received her last dose of QNEXA on 16 Mar 2008, 2 days before her myocardial infarction.

On 18 Mar 2008, the subject presented to the hospital with complaints of significant chest pain and was admitted for evaluation and treatment. On that same date, a cardiac catheterization revealed 80% stenosis of the left main stem coronary artery and an echocardiogram revealed akinesis of the interventricular septum and a mildly decreased ejection fraction of 40% to 45%. Laboratory testing revealed creatine kinase (CK) of 255 U/L, creatine kinase-myocardial band (CK-MB) of 29 U/L with CK-MB 11% of total CK, and a peak troponin I of 3.25 ng/mL. The subject was diagnosed with a myocardial infarction. Her vital signs and electrocardiogram results at approximately the same time as the event are shown in the table below, with corresponding data from the baseline visit for comparison.

Parameter	Baseline Values 19 Jan 2008	Approximate Time of Event Values (18 Mar 2008)
Weight, kg	91.9	88.7
BMI, kg/m^2	37.52	36.22
Blood pressure, mm Hg	122/78	112/76
RR, msec	982	NA
PR, msec	NA	174
QRS, msec	98	94
QT, msec	408	518
QTc, msec	NA	495
Overall interpretation	Normal	NA

BMI=body mass index; ECG=electrocardiogram; NA=not available; PR=period in the tracing of the ECG between the start of the P wave and the end of the R wave; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; QTc=QT interval corrected for heart rate; RR=period in the tracing of the ECG between the two R waves.

Treatment of the event included a percutaneous coronary intervention with a drug-eluting stent to the ostial proximal left anterior descending coronary artery. Treatment medications included ramipril, aspirin, metoprolol, atorvastatin, and clopidogrel.

Abnormal grade I/VI murmur and faint systolic murmur were noted on the physical examination performed at study entry on 19 Jan 2008. No changes were detected on the physical examination performed at the early termination visit on 14 Jun 2008. The investigator considered the myocardial infarction to be severe in intensity and not related to study drug. The subject recovered, and the event was considered resolved on 18 Mar 2008. The subject withdrew consent and completed the last study visit on 14 Jun 2008.

OB-303 / Subject 102-012 – QNEXA Mid dose
MACE: Myocardial infarction

A 67-year-old overweight (body mass index [BMI] 29.81 kg/m^2) Caucasian male experienced a myocardial infarction approximately 4 months after being randomized to QNEXA in OB-303. His relevant current medical conditions included type 2 diabetes and dyslipidemia. His past medical history included cigarette smoking, which he quit in 1965. No cardiac abnormalities were noted on his physical examination at study entry. Concomitant medications at the time of the event included metformin, tamsulosin, chromium picolinate, and aspirin.

The subject was randomized to QNEXA Mid dose on 28 Dec 2007. Study drug was permanently discontinued on 24 Apr 2008 because of the myocardial infarction.

On 24 Apr 2008, after pushing a hand mower about 150 feet, the subject became lightheaded and lethargic and was admitted to the hospital with a 2-day history of weakness, malaise, and some epigastric discomfort. An initial troponin was elevated at 39.67 with a creatine kinase (CK) of 783 and creatine kinase-myocardial band (CK-MB) of 61.9 (units and normal ranges not reported). An electrocardiogram (ECG) revealed inferior ST-segment elevation with anterior and anteroseptal ST depression. The subject was subsequently diagnosed with a myocardial infarction. His vital signs and ECG results at approximately the same time as the event are shown in the table below, with corresponding data from the baseline visit for comparison.

Parameter	Baseline Values 28 Dec 2007	Approximate Time of Event Values (24 Apr 2008)
Weight, kg	91.3	83.4
BMI, kg/m^2	29.81	27.23
Blood pressure, mm Hg	132/84	103/63

Parameter	Baseline Values 28 Dec 2007	Approximate Time of Event Values (24 Apr 2008)
Heart rate, bpm	98	85
RR, msec	606	NA
QRS, msec	92	NA
QT, msec	318	NA
Overall interpretation	Normal	Normal sinus rhythm, normal axis, inferior ST-segment elevations with nondiagnostic Q waves, anterior/anteroseptal ST-segment depression suggesting possible posterior involvement

BMI=body mass index; ECG=electrocardiogram; NA=not available; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

A coronary angiography demonstrated severe multivessel coronary artery disease with an occluded right posterolateral branch. During the angiography, the subject developed hemodynamic instability including heart block requiring placement of a temporary pacemaker and hypotension requiring intravenous dopamine and placement of an intrathoracic balloon pump. Treatment of the event included emergent bypass grafting times four: the left internal mammary artery to the left anterior descending coronary artery and reverse autogenesis saphenous vein grafts to the second obtuse marginal, right posterior descending artery, and right posterolateral arteries. The subject recovered from the event and was discharged from the hospital on 29 Apr 2008. He continued in the study off study drug.

The investigator considered the myocardial infarction to be severe in intensity and not related to study drug.

OB-303 / Subject 131-042 – QNEXA Top dose
MACE: Myocardial infarction

A 68-year-old obese (body mass index [BMI] 37.88 kg/m^2) Caucasian male experienced a myocardial infarction approximately 11 months after being randomized to QNEXA in OB-303. His relevant current medical conditions included sleep apnea syndrome and idiopathic edema. His past medical history included cigarette smoking, which he quit in 1964. No cardiac abnormalities were noted on his physical examination at study entry. Concomitant medications at the time of the event included fluticasone, acetaminophen, furosemide, diclofenac, and doxazosin.

The subject was randomized to QNEXA Top dose on 5 Feb 2008. Study drug was interrupted from 02 Jan 2009 to 11 Feb 2009. He received his last dose of study drug on 17 Mar 2009, and completed the study the following day.

On 11 Jan 2009, the subject presented to the emergency room after having an episode of chest pain. His vital signs and electrocardiogram (ECG) results at approximately the same time as the event are shown in the table below, with corresponding data from the baseline visit for comparison.

Parameter	Baseline Values 05 Feb 2008	Approximate Time of Event Values (11 Jan 2009)
Weight, kg	114.3	95
BMI, kg/m^2	37.88	31.49
Blood pressure, mm Hg	124/74	125/63
Heart rate, bpm	57	68
RR, msec	1052	NA
QRS, msec	96	NA
QT, msec	404	NA
Overall interpretation	Normal	Sinus rhythm, rate 60 bpm and normal axis

BMI=body mass index; ECG=electrocardiogram; NA=not available; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

The following day, initial troponin was 0.24 ng/mL (normal range, <0.10 ng/mL) and subsequent troponin was 6.62 ng/mL at 6:45 and 23.22 ng/mL at 23:18. The subject was subsequently transferred to another hospital and underwent a cardiac catheterization, which revealed triple vessel coronary artery disease and a left ventricular ejection fraction of 50%. On 13 Jan 2009 troponin was 17.41 ng/mL. The subject was diagnosed with a myocardial infarction. On that same date, an ECG showed normal sinus rhythm with a ventricular rate of 64 bpm. On 14 Jan 2009, the subject underwent an off-pump coronary artery bypass graft surgery times six with intramyocardial ramus branch. Treatment of the event included potassium, oxygen at 2

liters via nasal cannula, hydrocodone-acetaminophen, diltiazem, pravastatin, metoprolol, and clopidogrel. The subject recovered from the event with sequelae of a sternotomy incision and was discharged from the hospital on 18 Jan 2009.

The investigator considered the myocardial infarction to be severe in intensity and not related to study drug.

OB-303 / Subject 156-021 – QNEXA Top dose
MACE: Acute to subacute nonhemorrhagic infarct (neurologic)

A 52-year-old obese (body mass index [BMI] 35.52 kg/m^2) Caucasian female experienced a serious adverse event of acute to subacute nonhemorrhagic infarct approximately 11 months after being randomized to QNEXA in OB-303. Her relevant medical history included hypertension; dyslipidemia; hand numbness, left rib, neck, heel, leg, lower back, and left jaw pain; chest, abdominal, and right eye discomfort; left ear discomfort and pain and headaches. The subject was also a smoker, averaging 10 cigarettes/day. No cardiac or neurologic abnormalities were noted on her physical examination at study entry. Concomitant medications at the time of the event included atenolol, zolpidem, and propoxyphene-acetaminophen.

The subject was randomized to QNEXA Top dose on 24 Dec 2007. Study drug was interrupted on 27 Nov 2008 for 2 days because of the cerebral infarction. She received her last dose of study drug on 15 Jan 2009 and completed the trial the following day.

On 25 Nov 2008, the subject presented to the emergency room with expressive aphasia, slurred speech, word-finding difficulty, and left facial numbness. She reported having speech problems and confusion for 2 to 3 days prior to this date. An initial computed tomography scan was negative. A magnetic resonance imaging of the head was positive for an acute to subacute nonhemorrhagic infarct of the right corona radiate extending to the right basal ganglia. Magnetic resonance angiographies of the head and neck, including the carotid and vertebral arteries, and two-dimensional echocardiography were normal and indicated no stenosis or aneurysm. The subject's weight, BMI, and overall electrocardiogram interpretation at approximately the same time as the event are shown in the table below, with corresponding data at study baseline for comparison.

Parameter	Baseline Values 24 Dec 2007	Approximate Time of Event Values (25 Nov 2008)
Weight, kg	88.1	74.3
BMI, kg/m^2	35.52	29.95
Blood pressure, mm Hg	124/78	110-130s/80s
Heart rate, bpm	76	70s
RR, msec	881	NA
QRS, msec	86	NA
QT, msec	416	NA
Overall interpretation	Abnormal, NCS	Normal sinus rhythm, axis deviation, no acute ST-segment or T-wave changes

BMI=body mass index; ECG=electrocardiogram; NA=not available; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; NCS=neurocardiogenic syncope; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

Treatment of the event included lorazepam, enalapril, zolpidem, pantoprazole, ondansetron, ipratropium, docusate sodium, aspirin, alprazolam, albuterol, acetaminophen, simvastatin, and heparin. On 27 Nov 2008, the subject was discharged from the hospital. On 01 Dec 2008, the subject presented to the emergency room with right-sided changes in sensation and aphasia. Magnetic resonance imaging indicated no new infarct and the subject was discharged on the same date. She recovered from the event on 03 Dec 2008 and continued in the study.

The investigator considered the acute to subacute nonhemorrhagic infarct to be severe in intensity and not related to study drug.

OB-303 / Subject 188-052 – QNEXA Top dose
MACE: Myocardial infarction

A 52-year-old obese (body mass index [BMI] 34.3 kg/m^2) Caucasian female experienced a myocardial infarction approximately 6 months after being randomized to QNEXA in OB-303. Her relevant current medical conditions included hypertension, sleep apnea, and smoking (average of 10 cigarettes/day). A cardiac catheterization performed in 2005 was negative. No cardiac abnormalities were noted on her physical examination at study entry. Concomitant medications at the time of the event included losartan-hydrochlorothiazide, diclofenac, and zolpidem.

The subject was randomized to QNEXA Top dose on 28 Feb 2008. Study drug was permanently discontinued on 19 Aug 2008 because of the myocardial infarction. The subject continued in the study off study drug, and was considered lost to follow-up on 10 Nov 2008.

On 19 Aug 2008, the subject developed chest pain and was transported to the hospital via emergency medical services. During transport, she had a seizure and subsequently developed ventricular fibrillation without a pulse. Cardiopulmonary resuscitation was initiated. The subject reportedly experienced ventricular fibrillation or pulseless electrical activity for 23 to 24

minutes. On admission, her blood pressure was 140/70 mm Hg and her pulse was 122 bpm. Her weight, BMI, pulse, and blood pressure at approximately same time as the event are shown in the table below, with corresponding data at study baseline for comparison.

Parameter	Baseline Values 28 Feb 2008	Approximate Time of Event Values (19 Aug 2008)
Weight, kg	91.7	79
BMI, kg/m^2	34.3	29.55
Blood pressure, mm Hg	148/79	140/70
Heart rate, bpm	78	122
RR, msec	780	NA
QRS, msec	80	NA
QT, msec	368	NA
Overall interpretation	Normal	ST elevation in the precoridal leads and in leads I and aVL, and ST depression in inferior leads. Repeat ECG showed resolution of the ST elevation

BMI=body mass index; ECG=electrocardiogram; NA=not available; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

The subject was decorticating, was unresponsive, and was intubated. A computed tomography of the head performed on arrival at the emergency room revealed no bleeding and no gross abnormalities. Electrocardiogram results are shown in the table above. Laboratory results revealed a troponin I of 11.6 ng/dL, creatine kinase (CK) of 490 U/L, and creatine kinase-myocardial band (CK-MB) of 23.5 ng/mL. The subject was subsequently diagnosed with a myocardial infarction. On 20 Aug 2008, the subject underwent an echocardiogram, which showed mildly reduced left ventricular systolic dysfunction with regional wall motion abnormalities, distal anterior and mid to distal septal walls consistent with infarct, mild concentric left ventricular hypertrophy, and evidence of diastolic dysfunction. On 21 Aug 2008, the subject underwent revascularization of the proximal left anterior descending artery with drug-eluting stent placement. Additional treatment of the event included abciximab, heparin, furosemide, clopidogrel, aspirin, metoprolol, and diazepam. The subject recovered with sequelae from the event and was discharged from the hospital on 25 Aug 2008.

The investigator considered the myocardial to be severe in intensity and not related to study drug.

OB-303 / Subject 199-037 – QNEXA Top dose

MACE: Acute coronary syndrome and angina pectoris

A 64-year-old obese (body mass index [BMI] 33.77 kg/m^2) Caucasian male experienced a serious adverse event of acute coronary syndrome approximately 10 months after being randomized to QNEXA in OB-303. Two months later, he was hospitalized for angina pectoris. His relevant current medical conditions included dyslipidemia and asthma. The subject's past medical history was significant for smoking (average 60 cigarettes/day), which he quit in 1976. No cardiac abnormalities were noted on his physical examination at study entry. Concomitant medications at the time of acute coronary syndrome included diphenhydramine, meclizine, alfuzosin, fluticasone-salmeterol, azelastine, lovastatin, aspirin, ipratropium, and montelukast. At the time of onset of angina pectoris, the subject was also receiving nitroglycerin, budesonide-formoterol, ezetimibe, rosuvastatin, and ticlopidine.

The subject was randomized to QNEXA Top dose on 01 Apr 2008. Study drug was interrupted for 1 day on 28 Mar 2009 because of the angina pectoris. The subject received the last dose of study drug on 26 Apr 2009 and completed the study 2 days later.

On 14 Jan 2009, the subject experienced intermittent sharp chest pain and presented to the emergency room for evaluation and treatment. On that same date, he underwent a cardiac single-photon emission computed tomography stress test, which revealed possible reversible ischemia. An electrocardiogram (ECG) revealed a possible high lateral myocardial infarction and a second ECG revealed an anterolateral infarct (age undetermined). Laboratory testing revealed a creatine kinase (CK) of 80 IU/L, creatine kinase-myocardial band (CK-MB) of 2.5 ng/mL, and two troponin tests that were indeterminate at 0.5 ng/mL and 0.6 ng/mL (normal ranges not reported). The subject was discharged from the emergency room on a beta-blocker, with a recommendation to follow up with his primary care physician. On 23 Jan 2009, the subject was admitted to the hospital for the cardiac catheterization, which revealed diffuse atherosclerotic plaquing throughout the coronary tree and a high-grade lesion in the first diagonal suitable for intervention. The subject was subsequently diagnosed with coronary artery disease and underwent single-vessel balloon angioplasty of the diagonal artery. Additional treatment of the event included metoprolol, clopidogrel, and nitroglycerin. The subject recovered from the event on 24 Jan 2009 and was discharged from the hospital on that same date. Study drug was continued and the subject continued in the study.

On 26 Mar 2009, the subject experienced chest pain on exertion. On 28 Mar 2009, he experienced the same pain two or three times associated with elevated blood pressure, warmth, and flushing. On the same date, the subject went to the emergency room and was admitted for observation. Vital signs included blood pressure of 122/72 mm Hg and heart rate of 66 bpm. The physical examination was within normal limits, and a chest X-ray and electrocardiogram (ECG) were unremarkable. Laboratory tests included CK of 122 IU/L, CK-MB of 3.0 ng/mL, and troponin I of 0.03 ng/mL (normal ranges not reported). Treatment of the event included nitroglycerin, heparin, metoprolol, and isosorbide mononitrate. On 29 Mar 2009, he was discharged from the hospital. On 31 Mar 2009, a myocardial perfusion stress test revealed angina pectoris. On 16 Apr 2009, the subject was admitted to the hospital for a left heart catheterization procedure with left ventriculography and coronary angiography. Coronary angiography found restenosis of the first diagonal branch of the left anterior descending artery, which was revascularized following the placement of three TAXUS® drug-eluting stents. The subject

recovered from the event and was discharged from the hospital on 17 Apr 2009. His weight, BMI, and available ECG data at approximately the same time as events, respectively, are shown in the table below, with corresponding data at study baseline for comparison.

Parameter	Baseline Values 01 Apr 2008	Approximate Time of 1st Event (Acute Coronary Syndrome) Values (14 Jan 2009)	Approximate Time of 2nd Event (Angina Pectoris) Values (26 Mar 2009)
Weight, kg	109.4	80.6	79.2
BMI, kg/m^2	33.77	24.88	24.44
Blood pressure, mm Hg	138/92	128/80	160/80
Heart rate, bpm	76	58	66
PR, msec	NA	184	184
RR, msec	782	NA	NA
QRS, msec	94	90	94
QT, msec	390	440	388
QTc, msec	NA	432	410
Overall interpretation	Normal	P-R-T axes 74, 72, 72 possible high lateral myocardial infarction of undetermined age, sinus bradycardia	Normal with a normal sinus rhythm and a ventricular rate of 67 bpm

BMI=body mass index; ECG=electrocardiogram; NA=not available; PR=period in the tracing of the ECG between the start of the P wave and the end of the R wave; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; QTc=QT interval corrected for heart rate; RR=period in the tracing of the ECG between the two R waves.

The investigator considered the acute coronary syndrome to be severe in intensity and not related to study drug. The investigator considered the angina pectoris to be moderate in severity and not related to study drug.

OB-202 / Subject 0633 – Placebo
MACE: Thalamic infarction

A 38-year-old obese (body mass index [BMI] 44.6 kg/m^2) African American female with type 2 diabetes experienced a right thalamic stroke 21 days after receiving her last dose of placebo in OB-202. The subject's medical history was remarkable for type 2 diabetes since Dec 2000 and hypertension since 2002. Her relevant concomitant medications included metformin, metoprolol, and benazepril.

The subject was randomized to placebo on 23 Aug 2007 and received first dose on Aug 30. She received her last dose of placebo on 08 Sep 2007 and withdrew from the study on 11 Oct 2007.

On 29 Sep 2007, the subject experienced lightheadedness and left-sided numbness in the face and extremities. Approximately 9 hours after the onset of symptoms, she presented to the emergency room and was admitted to the hospital. She denied loss of consciousness, head injury,

headaches, blurred vision, dysphasia, chest pain, or palpitations. The subject was given oxygen, saline, and aspirin. A carotid ultrasound performed on 29 Sept 2007 showed 20% to 40% stenosis in both internal carotid arteries and magnetic resonance imaging of the brain performed on 30 Sept 2007 showed a right-sided lacunar thalamic infarct.

The subject's diabetes was managed with insulin during the hospitalization. She was referred for physical and occupational therapy, and she was discharged from the hospital on 02 Oct 2007, at which time the event was considered resolved.

A physical examination performed at the early termination visit on 11 Oct 2007 was unchanged from the examination performed at study entry on 23 Aug 2007 with the exception of mild weakness in left-sided grip strength, hip flexion, and left toe extension. No obvious sensory deficit was noted. The investigator considered the thalamic infarction to be mild in intensity and not related to study drug.

OB-303 / Subject 108-043 – Placebo
MACE: Coronary artery disease

A 63-year-old obese (body mass index [BMI] 42.45 kg/m^2) Caucasian female experienced a serious adverse event of coronary artery disease approximately 1 month after being randomized to placebo in OB-303. Her relevant current medical conditions included hypertension and dyslipidemia. Her past medical history included cigarette smoking (2 cigarettes/day), which she quit in 2001. No cardiac abnormalities were noted on her physical examination at study entry. Her relevant concomitant medications at approximately the same time as the event included conjugated estrogens and amlodipine + benazepril.

Parameter	Baseline Values 19 Feb 2008	Approximate Time of Event Values (17 Mar 2008)
Weight, kg	105.3	104
BMI, kg/m^2	42.45	42.92
Blood pressure, mm Hg	135/76	120-150/76
Heart rate, bpm	81	60-70
RR, msec	800	NA
PR, msec	NA	154
QRS, msec	89	90
QT, msec	396	426
QTc, msec	NA	466
Overall interpretation	Normal	Normal sinus rhythm, normal electrocardiogram

BMI=body mass index; ECG=electrocardiogram; NA=not available; PR=period in the tracing of the ECG between the start of the P wave and the end of the R wave; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; QTc=QT interval corrected for heart rate; RR=period in the tracing of the ECG between the two R waves.

The subject was randomized to placebo on 19 Feb 2008. Study drug was interrupted on 12 Mar 2008 because of the angina pectoris and was resumed on 20 Mar 2008. The subject received her last dose of study drug on 15 Mar 2009, and she completed the study the following day.

On 17 Mar 2008, the subject presented to the emergency room with complaints of severe jaw pain and angina and she was admitted to the hospital for evaluation and treatment. An electrocardiogram (ECG) and a cardiac stress test were normal. Cardiac catheterization revealed an 80% focal lesion in the right mid to proximal right coronary artery, which indicated coronary artery disease. The subject underwent stenting of the right coronary artery with two Cypher® drug-eluting stents on that same date. Her vital signs and ECG results at the time of the event are shown in the table below, with corresponding data from the baseline visit for comparison.

The subject was treated with clopidogrel, metoprolol, heparin, nitroglycerin, and isosorbide mononitrate. She recovered from the event and was discharged from the hospital on 18 Mar 2008. The study drug was interrupted and the subject continued in the study.

The investigator considered the coronary artery disease was considered by to be severe in intensity and not related to study drug.

OB-303 / Subject 124-040 – Placebo
MACE: Brain stem infarction

A 57-year-old obese (body mass index [BMI] 33.19 kg/m^2) Caucasian female experienced severe adverse events of transient ischemic attack (TIA) and a brain stem infarction approximately 8 months after being randomized to placebo in OB-303. Her relevant current medical conditions included type 2 diabetes and asthma. Her past medical history was significant for hypothyroidism, anxiety, and depression. Concomitant medications included fluticasone + salmeterol, albuterol, montelukast, and metformin.

The subject was randomized to placebo on 25 Jan 2008. Study drug was permanently discontinued on 8 Oct 2008 because of the TIA.

On 08 Oct 2008, the subject reported that she felt that she had a "bug" in her left eye; someone looked at the subject's eyes and saw an exophoria. She was taken to the local emergency room for evaluation and treatment of a TIA. On the way to the emergency room, she reported a loss of right-sided function. Assessment revealed a temperature of 97.3°F, pulse of 79 bpm, respirations of 20, blood pressure of 152/72 mm Hg, and oxygen saturation of 100% on 4 liters via nasal cannula. Physical examination revealed that pupils were equal, round, and reactive to light and accommodation, extraocular muscles were intact. On admission, the subject was awake, alert, oriented times three, and able to move all extremities. Her right upper and lower extremity strengths were 3 to 4/5 and the left extremity strengths were preserved. An electrocardiogram was normal. On the same date, a computed tomography (CT) scan of the head without contrast did not identify an acute intracranial bleed or an acute large vessel stroke. There were mild to moderate periventricular white matter small vessel ischemic changes and a few age-indeterminate lacunar infarcts present in the left basal ganglia. A neurologic consultation was obtained; on examination, the subject was noted to have a mild right facial droop, dysarthria, and gaze palsy to the left side. Tongue and uvula were noted to be midline. The motor examination demonstrated a right hemiparesis. The subject's left side showed no motor deficits, and the sensory examination was normal. The neurologic impression was acute stroke, with right hemiparesis, dysarthria, and gaze palsy to the left side, which was likely a left brain stem stroke. Intravenous heparin was initiated and the hemiparesis resolved within 3 hours of the onset. On 08 Oct 2008, the subject recovered from the TIA. Magnetic resonance imaging (MRI) of the brain without contrast showed no acute hemorrhage, infarct, or mass. An echocardiogram was performed and revealed mild left atrial enlargement and normal left ventricular wall motion. No thrombus or other cardiac source of cerebrovascular accident (CVA) was seen. On 09 Oct 2008, progress notes indicated that the right-sided weakness, dysarthria, and left-sided gaze palsy had clinically resolved; and the subject was discharged from the hospital on aspirin and with a prescription for extended-release dipyridamole.

On 10 Oct 2008, 2 days after the last dose of study drug, the subject started to mix up her words and experienced weakness on her right side. She was taken to the emergency room for evaluation and treatment. A CT scan revealed possible CVA in evolution, and the subject was admitted to the hospital and started on intravenous heparin. An MRI of the brain showed a left CVA. On 11 Oct 2008, an MRI of the brain revealed a new brain stem infarct and multiple areas of T2 hypersensitivity in deep subcortical white matter, most likely indicative of gliosis. Treatment included aspirin, dipyridamole, and simvastatin. On 17 Oct 2008, the subject was discharged to

acute rehabilitation with continued physical, speech, and occupational therapy. Neurologic examination revealed a persistent slight right facial droop, dysarthria, and right upper extremity weakness greater distally than proximally. On 18 Oct 2008, the subject's prothrombin time was 12.3 seconds and international normalized ratio (INR) was 0.9. On 20 Oct 2008, physical therapy cleared the subject for ambulation with a cane, and the subject's endurance and gait improved. Prior to discharge, the subject was able to perform her activities of daily living independently. She was discharged home and was discontinued from the study on 30 Oct 2008 because of the TIA. Her weight and vital signs at the approximate time of the brain stem infarction are shown in the table below, with corresponding data from the baseline visit for comparison.

Parameter	Baseline Values 25 Jan 2008	Approximate Time of Event Values (10 Oct 2008)
Weight, kg	83.9	79
BMI, kg/m^2	33.19	31.25
Blood pressure, mm Hg	138/82	155/77
Heart rate, bpm	74	68
BMI=body mass index.		

The subject recovered with sequelae from a brain stem infarction on 10 Oct 2008. The subject's neurologic examination at study termination on 30 Oct 2008 revealed decreased right wrist dorsiflexion, decreased biceps strength, and right arm abduction as consequences of the CVA.

The investigator considered the events of TIA and a brain stem infarction to be moderate in severity and not related to study drug.

OB-303 / Subject 130-050 – Placebo
MACE: Coronary artery disease

A 65-year-old obese (body mass index [BMI] 30.76 kg/m^2) Caucasian male experienced left main coronary disease approximately 5 months after being randomized to placebo in OB-303. His relevant current medical conditions included dyslipidemia and cigarette smoking (average 20 cigarettes/day). The subject also reported frequent coughing, shortness of breath, and sleep apnea. No cardiac abnormalities were noted on his physical examination at study entry. His concomitant medications at the time of the event included simvastatin and aspirin.

The subject was randomized to placebo on 30 Jan 2008. Study drug was permanently discontinued on 12 Jun 2008 because of the coronary artery disease, and the subject withdrew from the study on 23 Jul 2008.

On 09 Jun 2008, the subject presented to the cardiologist with complaints of exertional chest pain. He underwent a cardiac stress test, which revealed a large anteroseptal area of ischemia, suggesting an abnormality in the left anterior descending territory. Left ventricular systolic function showed mild septal hypokinesis and an ejection fraction of 61%. The subject was admitted to the hospital on 13 Jun 2008. Cardiac catheterization revealed significant coronary disease with good ventricular function. His vital signs and electrogram results at the time of the event were not available. On 16 Jun 2008, the subject underwent coronary bypass grafting of the left internal mammary artery to the left anterior descending artery and a saphenous vein graft to the obtuse marginal branch. He recovered from the event and was discharged from the hospital on 20 Jun 2008. In addition to the coronary artery bypass graft, he was treated with metoprolol and oxycodone-acetaminophen. The subject recovered and the coronary artery disease was considered resolved on 20 Jun 2008.

The investigator considered the coronary artery disease to be moderate in intensity and not related to study drug.

OB-303 / Subject 143-037 – Placebo
MACE: Cardiopulmonary arrest (Death)

A 44-year-old obese (body mass index [BMI] 34.57 kg/m^2) Caucasian male died after experiencing cardiopulmonary arrest approximately 2 months after being randomized to placebo in OB-303. His relevant current medical conditions included hypertension and anxiety disorder. No cardiac abnormalities were noted on his physical examination at study entry. His concomitant medications at the time of the event included lisinopril-hydrochlorothiazide and citalopram.

The subject was randomized to placebo on 27 Feb 2008. Study drug was permanently discontinued on an unknown date.

On 22 Apr 2008, the subject was found unresponsive and emergency medical services were called. On arrival of emergency medical services, the subject was noted to be apneic and pulseless. After receiving unspecified treatment by emergency medical services en route to the hospital, the subject spontaneously regained a pulse. He was subsequently admitted to the hospital for neurologic evaluation. On hospital admission, he was intubated and placed on a ventilator. Neurologic examination revealed the subject to be unresponsive to physical stimuli. Pupils were mid position and reactive. There was no gaze preference, no corneal reflex, and no gag reflex. Extremities were flaccid, reflexes were not elicitable, and toes were mute. Electroencephalogram (EEG) showed suppression with bursts at 2 to 3 cycles per second followed by prolonged suppression. A subsequent EEG was also nonreactive. No evidence of sleep was seen. Urine drug screen was positive for cocaine. On 23 Apr 2008, the subject's creatine kinase-myocardial band fraction (CK-MB) was elevated to 10.81 ng/mL and further increased to 20.0 ng/mL. Troponin I was also elevated to 0.14 and further increased to 0.221. On 24 Apr 2008, a chest X-ray revealed new bilateral interstitial infiltrates in both lower lung zones, right greater than left. Treatment of the event included norepinephrine, propofol, atropine, and epinephrine. The subject never regained consciousness and subsequently died as a result of cardiopulmonary arrest on 24 Apr 2008. Additional diagnoses at the time of death included poly-substance abuse and anoxic/toxic metabolic encephalopathy.

The investigator considered the cardiopulmonary arrest to be severe in intensity and not related to study drug.

OB-303 / Subject 151-079 – Placebo
MACE: Coronary artery disease

A 48-year-old obese (body mass index [BMI] 37.02 kg/m^2) Caucasian male experienced a serious adverse event of coronary artery disease approximately 7 weeks after being randomized to placebo in OB-303. His relevant current medical conditions included coronary artery disease with medicated stent placement (2005), dyslipidemia (2000), and sleep apnea (2002). No cardiac abnormalities were noted on his physical examination at study entry. His concomitant medications at the time of the event included ezetimibe, and the following medications that he was taking for coronary artery disease prophylaxis: metoprolol, rosuvastatin, aspirin, and clopidogrel.

The subject was randomized to placebo on 18 Mar 2008. Study drug was permanently discontinued on 8 May 2008 due to coronary artery disease, and the subject withdrew from the study on 17 Feb 2009.

On 08 May 2008, the subject presented to the emergency room with complaints of right-sided chest pain and was admitted to the hospital for evaluation and treatment. His weight, BMI, and overall electrocardiogram (ECG) results at the approximate time of the event are shown in the table below, with corresponding data from study baseline for comparison.

Parameter	Baseline Values 18 Mar 2008	Approximate Time of Event Values (8 May 2008)
Weight, kg	137.9	135.5
BMI, kg/m^2	37.02	36.38
Blood pressure, mm Hg	113/79	NA
Heart rate, bpm	55	84
RR, msec	1118	NA
QRS, msec	104	106
QT, msec	428	366
Overall interpretation	Abnormal, NCS	Normal sinus rhythm and incomplete bundle branch block

BMI=body mass index; ECG=electrocardiogram; NA=not available; NCS=neurocardiogenic syncope; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

Laboratory testing revealed a creatine kinase (CK) of 152 U/L, creatine kinase-myocardial band (CK-MB) of 2.0 ng/mL, and troponin of 0.03 ng/mL (normal ranges not reported). A computed tomography angiogram of the chest showed coronary artery calcifications and mild dilation of the ascending thoracic aorta, with no dissection, pulmonary embolus, or acute pulmonary disease. An ECG revealed normal sinus rhythm and incomplete bundle branch block. On 09 May 2008, the subject's CK was 110 U/L, CK-MB was 1.4%, and troponin was 0.03 ng/mL. On 12 May 2008, CK was 62 U/L and CK-MB was 1.6%. That same day, the subject underwent a cardiac catheterization with coronary arteriography. An 80% stenosis of the mid left anterior descending artery was noted and a drug-eluting stent was successfully placed. The subject

recovered with sequelae from the event and was discharged from the hospital on 13 May 2008. Treatment of the event included midazolam, fentanyl, lidocaine, aspirin, clopidogrel, bivalirudin, nitroglycerin, and normal saline.

The investigator considered the coronary artery disease to be severe in intensity and not related to study drug.

OB-303 / Subject 193-032 – Placebo
MACE: Coronary artery disease

A 60-year-old obese (body mass index [BMI] 32.04 kg/m^2) Caucasian female experienced a serious adverse event of coronary artery disease approximately 2 months after being randomized to placebo in OB-303. Her relevant current medical conditions included hypertension, dyslipidemia, and coronary arteriosclerosis. The subject's past medical history included angina pectoris and multiple angioplasties. No cardiac abnormalities were noted on her physical examination at study entry. Her concomitant medications at the time of the event included ezetimibe-simvastatin, aspirin, metoprolol, and losartan.

The subject was randomized to placebo on 12 Mar 2008. Study drug was permanently discontinued on 29 May 2008 because of the coronary artery disease, and the subject withdrew from the study on 12 Jun 2008.

On 15 May 2008, the subject experienced intermittent substernal chest pressure, which worsened with activity. On 30 May 2008, she was admitted to the hospital and underwent cardiac catheterization. Her weight and BMI at the time of the event are shown in the table below, with corresponding data at study baseline for comparison. Electrocardiogram (ECG) information at the approximate time of the event was not available, but baseline ECG data are shown in the following table.

Parameter	Baseline Values 12 Mar 2008	Approximate Time of Event Values (15 May 2008)
Weight, kg	75.4	75.4
BMI, kg/m^2	32.04	32.04
Blood pressure, mm Hg	128/66	NA
Heart rate, bpm	66	NA
RR, msec	938	NA
QRS, msec	88	NA
QT, msec	414	NA
Overall interpretation	Normal	NA

BMI=body mass index; ECG=electrocardiogram; NA=not available; QRS=deflections in the tracing of the ECG, comprising the Q, R, and S waves; QT=interval in the tracing of the ECG between the start of the Q wave and the end of the T wave; RR=period in the tracing of the ECG between the two R waves.

The subject was subsequently diagnosed with coronary artery disease and underwent a percutaneous transluminal coronary angioplasty with placement of three stents. She recovered

from the event on 30 May 2008 and was discharged from the hospital the following day. Additional treatments included clopidogrel and atorvastatin.

Coronary artery disease was considered by the investigator to be moderate in severity and not related to study drug.

12.7 Appendix 7: LEARN® Program for Weight Management

The LEARN® program is the most scientifically sound, safe and effective weight management program available today. Different from any other program available today, it teaches important skills necessary to live and maintain a healthy body weight in today's "toxic" environment of high-fat, high-calorie foods, and numerous labor-saving devices.

The latest edition of the LEARN program begins with an introduction and orientation lesson, followed by 12 weekly lessons and a commencement lesson. It also includes a master list of various lifestyle techniques, personal charts and forms, a fast food guide, calorie guide, a Weight Loss Readiness Test, and a comprehensive index.

Why LEARN?

The program is titled "LEARN" for two reasons. First, learning implies an educational process in which the person masters crucial information and applies it to everyday life. Secondly, the word LEARN is formed from the first letter of the five components of this program: Lifestyle, Exercise, Attitudes, Relationships and Nutrition.

Learning Healthy Behaviors

The LEARN program teaches people how to become students of their unique habits. LEARN participants learn when, how and why their habits occur, and more importantly, how to incorporate healthier behaviors into their daily lifestyle.

The LEARN program teaches key weight management principles and helps program participants develop individualized techniques for applying these principles to their daily lives. More than 200 specific lifestyle change techniques are discussed throughout 320 pages of text. The program's focus on permanent results is what separates it from all other weight management programs.

Key Topics

Key topics of the LEARN program are:

- Coping with lapse and preventing relapse
- Creative ways to stay motivated
- Dealing with pressures to eat
- Family and relationships
- Guidelines for setting reasonable weight loss goals
- Helpful tips for eating away from home
- How attitude can affect weight loss
- How to use the Food Guide Pyramid
- Information about body image and weight maintenance
- Multiple weight change records to track progress
- New information on exercise and physical activity
- Quality of Life Self-Assessments

The LEARN program was developed by Kelly D. Bronwell, Ph.D. LEARN is a registered trademark of American Health Publishing Co., Dallas, Texas.

12.8 Appendix 8: Baseline Characteristics of QNEXA Responders and Nonresponders

Table 46. Baseline Demographic Characteristics, Co-Morbidities, Subject Disposition, Treatment-Emergent Adverse Events, and Concomitant Medications in QNEXA Responders and Nonresponders (ITT Set, 1-Year Cohort)

Subgroup Analysis	Nonresponders QNEXA Total (N=800)	Responders QNEXA Total (N=1476)
Demographic and baseline characteristics		
Age, years (mean)	48.04*	48.31*
Sex, n (%)		
Male	215 (26.9)	374 (25.3)
Female	585 (73.1)	1102 (74.7)
Race/Ethnicity, n (%)		
Hispanic or Latino	149 (18.6)	195 (13.2)
Not Hispanic or Latino	651 (81.4)	1281 (86.8)
Caucasian	667 (83.4)	1247 (84.5)
African American	110 (13.8)	194 (13.1)
Asian	7 (0.9)	13 (0.9)
American Indian or Alaskan Native	8 (1.0)	15 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.1)	7 (0.5)
Other	11(1.4)	14 (0.9)
Weight, kg	107.88*	106.49*
Height, cm	167.04*	166.84*
Body mass index, kg/m^2	38.53*	38.13*
Co-morbidities at baseline		
Diabetic status		
Yes	124 (15.5)	182 (12.3)
No	676 (84.5)	1294 (87.7)
History of depression		
Yes	176 (22.0)	287 (19.4)
No	624 (78.0)	1189 (80.6)
Hypertension status		
Yes	308 (38.5)	615 (41.7)
No	492 (61.5)	861 (58.3)
Dyslipidemic status		
Yes	183 (22.9)	411 (27.8)
No	617 (77.1)	1065 (72.2)
Waist circumference, cm	115.63*	115.16*
Systolic blood pressure, mm Hg	125.9*	126*
Diastolic blood pressure, mm Hg	79.1*	79.3*
Heart rate, bpm	72.2*	72.7*
Total cholesterol, mg/dL	201.1*	199.6*
Low-density lipoprotein cholesterol, mg/dL		
N	798	1476
Mean	123.1	120.8
High-density lipoprotein cholesterol, mg/dL		
N	800	1476
Mean	49.2	49.1

Subgroup Analysis	Nonresponders QNEXA Total (N=800)	Responders QNEXA Total (N=1476)
Total cholesterol/high-density lipoprotein ratio		
N	800	1476
Mean	4.304	4.289
Triglycerides, mg/dL		
n	800	1476
Mean	144.3	148.7
ALT, mU/mL		
n	800	1476
Mean	29.3	30
AST, mU/mL		
n	800	1476
Mean	23.8	24.1
Hemoglobin Alc (%)		
n	505	1037
Mean	6.12	5.93
Fasting blood glucose (mg/dL)		
n	800	1470
Mean	105.5	103.4
Subject disposition [1]		
Completed all study visits	419 (52.4)	1243 (84.2)
Discontinued from study	381 (47.6)	233 (15.8)
Adverse event	92 (11.5)	47 (3.2)
Subject lost to follow-up	124 (15.5)	73 (4.9)
Requirement for restricted medications	7 (0.9)	6 (0.4)
Protocol noncompliance	11 (1.4)	9 (0.6)
Pregnancy	3 (0.4)	15 (1.0)
Lack of efficacy	4 (0.5)	3 (0.2)
Subject withdrew consent	115 (14.4)	65 (4.4)
Other	23 (2.9)	14 (0.9)
Completed all visits on study drug	312 (39.0)	1173 (79.5)
Discontinued study drug	488 (61.0)	303 (20.5)
Adverse event	225 (28.1)	134 (9.1)
Subject lost to follow-up	104 (13.0)	61 (4.1)
Requirement for restricted medications	5 (0.6)	5(0.3)
Protocol noncompliance	15 (1.9)	7 (0.5)
Pregnancy	3 (0.4)	14 (0.9)
Lack of efficacy	14 (1.8)	6 (0.4)
Subject withdrew consent	96 (12.0)	59 (4.0)
Other	24 (3.0)	16 (1.1)
Subjects with treatment-emergent adverse events by system organ class [2]		
Total, n (%)	666 (83.3)	1321 (89.5)
Infections and infestations	294 (36.8)	781 (52.9)
Investigations	56 (7.0)	139 (9.4)
Gastrointestinal disorders	294 (36.8)	695 (47.1)
Nervous system disorders	306 (38.3)	618 (41.9)
Musculoskeletal and connective tissue disorders	137 (17.1)	357 (24.2)
Psychiatric disorders	185 (23.1)	285 (19.3)
General disorders and administration-site conditions	147 (18.4)	271 (18.4)
Respiratory, thoracic, and mediastinal disorders	103 (12.9)	248 (16.8)
Eye disorders	128 (16.0)	211 (14.3)
Injury, poisoning, and procedural complications	64 (8.0)	229 (15.5)
Skin and subcutaneous tissue disorders	76 (9.5)	250 (16.9)

Subgroup Analysis	Nonresponders QNEXA Total (N=800)	Responders QNEXA Total (N=1476)
Metabolism and nutrition disorders	65 (8.1)	155 (10.5)
Vascular disorders	42 (5.3)	71 (4.8)
Reproductive system and breast disorders	34 (4.3)	120 (8.1)
Renal and urinary disorders	38 (4.8)	63 (4.3)
Cardiac disorders	33 (4.1)	45 (3.0)
Ear and labyrinth disorders	24 (3.0)	67 (4.5)
Immune system disorders	12 (1.5)	34 (2.3)
Neoplasm benign, malignant and unspecified (including cysts and polyps)	9 (1.1)	25 (1.7)
Blood and lymphatic system disorders	7 (0.9)	25 (1.7)
Hepatobiliary disorders	8 (1.0)	19 (1.3)
Endocrine disorders	3 (0.4)	15 (1.0)
Congenital, familial and genetic disorders	4 (0.5)	2 (0.1)
Social circumstances	1 (0.1)	6 (0.4)
Concomitant medications during the double-blind treatment period [3]		
Total	725 (90.6)	1409 (95.5)

*mean.
Includes data from studies OB-202, OB-302, and OB-303.
1. Subjects may be counted in both discontinuation sections.
2. Although a subject may have had two or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
3. Although a subject may have had two or more medications, the subject is counted only once within a category. Concomitant medications are defined as those used during the double-blind treatment period. The same subject may appear in different categories.
ALT=alanine transaminase; AST=aspartate transaminase; ITT=intent-to-treat; QNEXA=fixed-dose combination of phentermine (PHEN) and topiramate (TPM).
QNEXA Low dose, 3.75/23 mg; QNEXA Mid dose, 7.5/46 mg; QNEXA Top dose, 15/92 mg.

12.9 Appendix 9: Health Care Professional (HCP) and Patient Tools

Healthcare Provider (HCP) Tools

HCP Introductory Letter

The content of this introductory letter will focus on the Risk Evaluation and Mitigation Strategy (REMS) and risks associated with QNEXA, as well as the importance of appropriate patient selection. Specifically, this letter will address:

- Criteria for patient selection (body mass index [BMI] >30 or >27 kg/m^2 with co-morbid conditions)
- Appropriate dosing and titration guidelines
- Importance of using QNEXA in conjunction with a weight management program, including nutrition and physical activity
- Risks of depression, anxiety, suicidality, and cognitive events (eg attention/concentration and memory difficulties)
- Risks associated with pregnancy and the importance of contraception
- Role of the QNEXA Pregnancy Registry
- Risk of acute angle closure glaucoma and metabolic acidosis
- HCP educational webcast on QNEXA and obesity management
- Importance of the QNEXA Medication Guide

This letter will be sent to the following specialists at time of approval: Family/General Practitioners, Nurse Practitioners/Physicians Assistants, Endocrinologists, Internists, OBGyns, and Cardiologists. It will also be sent to pharmacists.

HCP Safety Brochure

The brochure will provide detailed information about the risks associated with QNEXA as outlined in the HCP Introductory letter (see above). In addition, this brochure will contain three items integral to the important messages of (1) dosing and titration guidelines, (2) proper patient selection, and (3) proper management of patients.

Dosing and Titration Card

To ensure that HCPs understand the importance of proper dosing and titration guidelines, a stand-alone card will be inserted into a pocket in the brochure. This content will include specific instructions for dosing and titration, illustrated with a schematic that highlights the proper schedule for initiation, assessments, maintenance, and reasons for discontinuation.

BMI Wheel

To support the HCP in their selection of appropriate patients, included in the brochure will be a tool for BMI calculations. In bold print at the bottom of the wheel, in an easy-to-read place, this text will appear: "Patients must have BMI >30 or >27 kg/m^2 with co-morbidities."

Patient Management Checklist

Another tool to support proper use of QNEXA will be a checklist that will graphically show the specifics involved in each patient assessment included weight, vitals, dosing, titration, risk discussions, and other requirements.

All HCP tools will be available on the QNEXA product website.

Patient Tools

Medication Guide

A Medication Guide will be packaged with each bottle of QNEXA. In addition, tear-off pads of Medication Guide will be distributed to pharmacists and HCPs.

Patient Information Packet

Along with the Medication Guide, patient-prescribed QNEXA will be provided with an informational packet that describes the risk of the product in patient-friendly language. This packet will be distributed to patients at the time of initiation of QNEXA and will include a Patient Brochure.

The QNEXA Patient Brochure outlines the key risk messages consistent with the Pregnancy Registry and the REMS, as well as the need for birth control and to stop QNEXA if pregnancy occurs. It stresses the signs and symptoms of depression, anxiety, suicidality, changes in cognitive function, acute narrow angle glaucoma, and metabolic acidosis. The brochure also stresses the need for a comprehensive weight management program including nutrition and physical exercise.

All patient tools will be available on the QNEXA website for the on-line patient support program.